STUDIUL UNOR MATERIALE CERAMICE POROASE PE BAZĂ DE HIDROXIAPATITĂ CA SUBSTITUTE OSOASE PENTRU CRANIOPLASTIE
STUDY ON POROUS HYDROXYAPATITE BASED CERAMIC MATERIALS AS BONE SUBSTITUTES FOR CRANIOPLASTY

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The study was focused on the development of some porous hydroxyapatite (HAp) based ceramic materials as bone substitutes for cranioplasty. The HAp samples were elaborated by a hot pressure casting technique at a casting temperature of 90°C and 5 atm pressure, having 77 wt.% HAp and 23 wt.% melted paraffin and bee wax binder. The samples were casted without and with the addition of 5 wt.% and 10 wt.% porogen agent. Then the cast samples were dried, dewaxed, and sintered at 1150°C, 1200°C, and 1250°C for 2 hours. The final sizes of the sintered samples were 10±0.05 mm in diameter and 40±0.3 mm in length. The structural properties were investigated by X-ray diffraction (XRD). The water absorption, apparent porosity and apparent density were determined by standard test methods for ceramics. The mechanical properties were investigated by flexural and compressive tests. The microstructure was analyzed by scanning electron microscopy (SEM). All the sintered samples revealed crystalline phases and homogeneous microstructure. The apparent density was 1.28-1.76 g/cm^3, the apparent porosity was 43-57 %, the flexural strength was 4-8.6 MPa, and the compressive strength was 5.4-13.7 MPa. The obtained results meet the technical requirements imposed for porous ceramics used in cranioplasty. The properties were enhanced with the increase of the sintering temperature but the addition of the porogen agent contributed to an increase of the apparent porosity and a decrease in mechanical strength. The samples sintered at 1250°C revealed the best properties that recommend the developed HAp materials for biomedical applications.

Acest studiu s-a axat pe dezvoltarea unor materiale ceramice pe bază de hidroxiapatită (HAp) poroasă ca substitute osoase pentru cranioplastie. Probele de HAp au fost elaborate printr-o tehnică de turnare sub presiune la cald, la o temperatură de turnare de 90°C și presiune de 5 atm, cu un conținut masic de 77 % HAp și 23 % liant (parafină și ceară de albine). Probele au fost turnate atât fără, cât și cu un adaos de agent porogen de 5%, respectiv 10%. Apoi, probele turnate au fost uscate, deparafinate și sinterizate la 1150°C, 1200°C și 1250°C timp de 2 ore. Dimensiunile finale ale probelor sinterizate au fost de 10±0.05 mm în diametru și 40±0.3 mm în lungime. Proprietățile structurale au fost investigate prin difracție de raze X (XRD). Absorbția apei, porozitatea aparentă și densitatea au fost determinate prin metode standard de testare a materialelor ceramice. Proprietățile mecanice au fost investigate prin teste de încovoiere și compresiune. Microstructura a fost analizată prin microscopie electronică cu scanare (SEM). Toate probele sinterizate au prezentat faze cristaline și microstructură omogenă. Densitatea a fost de 1,28-1,76 g/cm^3, porozitatea aparentă a fost de 43-57 %, rezistența la încovoiere a fost de 4-8,6 MPa, iar rezistența la compresiune a fost de 5,4-13,7 MPa. Rezultatele obținute se încadrează în cerințele tehnice impuse ceramicilor poroase utilizate în cranioplastie. Proprietățile au fost îmbunătățite odată cu creșterea temperaturii de sinterizare, dar adăugarea agentului porogen a contribuit la creșterea porozității aparente și la scăderea rezistenței mecanice. Probele sinterizate la 1250°C au prezentat cele mai bune proprietăți, fapt ce recomandă materialele HAp dezvoltate pentru aplicații biomedicale.

Keywords: *hydroxyapatite, biomaterials, hot pressure casting, porogen agent*

1. Introduction

Craniocerebral trauma and its sequelae must be a major public health problem in the industrialized world. Their incidence depends on socio-economic and cultural factors, constituting the main cause of post-traumatic deaths and the most frequent generator of permanent post-traumatic disability. The number of people who need surgery every year due to degenerative bone disease or bone destruction through trauma or aging is constantly increasing.

Currently, the growing social need for health (treatment and preservation) can be achieved by providing personalized medical services, through prevention measures, reducing medical costs and hospitalization periods, while increasing non-traumatic outpatient medical interventions and complete diagnostics for patients. Intensive research is conducted both to understand the phenomenon of "bone repair or healing" and to develop techniques for effective applications involved in bone regeneration. To achieve these goals, an important role belongs to the developers in the field of medical technologies [1 - 3].

Cranioplasty (surgery on the cranial bone system) should be safe and easy to handle. Over time, the skull reconstruction has shown limitations such as the performance of the materials used for implantation, poor cosmetic results, rejection of the materials used for reconstruction, prolonged surgery, and the need for multiple surgeries.

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Reconstruction of cranial bone defects is necessary if the defects exceed a critical size or when significant deformation is observed [4, 5]. In choosing the most suitable implant materials, the assessment of each case must be taken into account, depending on the size of the defect and the patient's condition [6]. In the case of small defects, 10-50 mm^2 cranial bone grafts or non-customized titanium mesh are used, while larger defects 50-100 mm^2 require autogenous bone or synthetic materials for reconstruction [7]. Bone substitutions or bone parts have been used for many centuries and the main dilemma for reconstruction with autogenic or synthetic materials has not yet been solved [8]. The materials currently used have different properties and therefore have different interactions with the host tissue [9-11]. Computer-made alloplastic implants have revolutionized the concept of bone reconstruction in patients who, for various reasons, have suffered a partial loss of the cranial cavity [12, 13]. The design allows doctors to create exact models for each defect, with predictable results and shorter surgery duration. The researchers designed various prototypes of cranial implants based on different types of cranial trauma. The geometries were initially generated by computed tomography (CT) scanning, and the mechanical properties of the alloplastic implant were adapted to the specific needs of the patient. The osseointegration and osteoconductivity characteristics of the implant were also considered.

The purpose of surgery is to use a prosthesis as close as possible as to the shape and size of a cranial defect, without the danger of infection or resorption, as well as a good aesthetic result [14, 15]. According to the above, Costantino and collaborators [8] consider that an ideal cranial implant must meet 8 requirements: (1) to be biocompatible; (2) to have sufficient mechanical strength for safe protection of the affected area; (3) to have a perfect contour, similar to the produced defect; (4) to be stable over time; (5) to cause a minimal inflammatory response; (6) to be radio-opaque for viewing during and after surgery; (7) to be non-allergic and non-carcinogenic; (8) to be a synthetic material, accessible, and easy to handle.

Currently, three types of cranioplasty procedures are practiced: (i) with autografts, (ii) with ad-hoc shaped biomaterials (mostly polymers), and (iii) with prefabricated custom-made prostheses using rapid prototyping techniques that include a full range of ceramic, plastic, or metal biomaterials. Starting with 2008, through the new radiology technologies and the appearance of new biomaterials, the 3D reconstruction was performed with the help of the CT, allowing the development of customized devices and even the 3D reconstruction of the cranium [16-18].

Bioceramics can be suitable materials, especially for patients who have undergone a failed initial treatment, and can be a good and effective alternative for the final reconstruction of large and complex cranial defects. Bioceramic implants have also shown good aesthetic results, and at the same time avoid the morbidity problems associated with the donor.

Ceramic biomaterials, and especially those based on calcium phosphates such as hydroxyapatite (HAp, $Ca_{10}(PO_4)_6(OH)_2$) and β-tricalcium phosphate (β-TCP) used in reconstructive bone surgery (maxillofacial or orthopedic), are structurally dense or porous products. Porosity, whether micro or macro-porosity, is an essential condition in the biological process of bone reconstruction. Macroporosity is defined by the presence of pores > 100 μm and represents the area where bone cells will grow, while microporosity, defined by the presence of pores of 1-10 μm is useful in the mineralization process-transport of biological substances.

The excellent biocompatibility of hydroxyapatite makes this material a promising candidate in the development of medical applications like bone substitutes for cranioplasty.

Cranial bone surgery is a research field dominated by the interest of neurosurgeons and engineers, urging them to constantly promote new technologies or materials [19-30]. The main technical requirements imposed for porous ceramics used in cranioplasty are the optimum sizes of the customized implant, good mechanical properties (i.e. Young's modulus of 2-15 GPa, compression strength of 10-50 MPa), apparent porosity of 10-40 %, along with proper bioactivity, antibacterial activity, osseointegration and osteoconductivity [22, 23].

In this study, we present the research results for the development of porous HAp based ceramic materials obtained by a hot pressure casting technology using a microcrystalline HAp powder and a binder (melted paraffin and bee wax) without and with the addition of a thermoplastic cellulose ether as a porogen agent and sintered at 1150°C, 1200°C, and 1250°C as potential candidates for bone substitutes. We used hot pressure casting since it is currently the most important process for shaping products with a complex configuration in the production of technical ceramics. The main advantages of the hot pressure casting technique consist in obtaining parts with complex shapes with very precise dimensions and with relatively uniform surfaces, which makes the molded parts to be used directly without further finishing operations, and achieving high productivity (reuse of waste in the technological flow) at relatively low cost prices.

The obtained HAp samples were characterized by XRD to identify the phases. The microstructure was analyzed by SEM.

Physical and mechanical tests were also performed to determine the influence of the sintering temperature and the addition of the porogen agent on the properties of the developed materials. These properties are important to be studied to qualify porous HAp based ceramic materials in biomedical applications since have to be found a balance between the apparent porosity and mechanical strength.

2. Experimental part

2.1. Materials and methods

The HAp powder with microcrystalline structure was synthesized by a wet chemical precipitation method using high purity calcium carbonate ($CaCO_3$) and calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$) as starting materials as described elsewhere [25]. Ceramic slurries of 77 wt.% HAp powder and 23 wt.% binder (melted paraffin and bee wax) were prepared without and with 5 wt.% and 10 wt.% porogen agent (Ethocel, particle size of 100-400 μm). Each ceramic slurry was cast in a mold using a hot pressure casting process performed at a temperature of the ceramic slip in the tank of 90°C, a pressure of 5 atm, and an injection duration of 10 seconds. After that, the HAp green samples were removed from the molds, deburred, and dried at room temperature for 48 h. Then, the samples were dewaxed at 600°C, and subsequently sintered at various temperatures (1150°C, 1200°C, and 1250°C) for 2 hours with a heating rate of 100 °C/h. The final sizes of the sintered samples were 10±0.05 mm in diameter and 40±0.3 mm in length.

2.2. Structural analysis by X-ray diffraction

X-ray diffraction investigation was performed with a Bruker D8 Discover instrument, in Bragg Brentano geometry, equipped with a 1D LynxEye detector and Cu source radiation, Kα of 1.5406 Å, voltage of 40 kV, intensity of 40 mA, at a scan speed of 1 s/step, and an increment of 0.04°. For the crystalline phase analysis was used the ICDD PDF2 Release 2015 database.

2.3. Analysis of microstructure

Scanning electron microscopy (SEM) was used to visualize the microstructure and the qualitative distribution of the granular phases and pores in the ceramic materials. The SEM analysis of the sintered materials was performed using a FESEM-FIB Auriga scanning electron microscope and a maximum acceleration voltage of 5 kV.

2.4. Determination of water absorption, apparent porosity and apparent density

The water absorption (A), apparent porosity (P_a) and apparent density (ρ_a) of the sintered samples were determined according to the SR EN 1389-2004 by Archimedes' principle using a Mettler Toledo hydrostatic balance, by successive weighing in air each dry sample and then immersed in distilled water. All the presented values are the mean values of 3 measurements. The water absorption, apparent porosity and apprent density were calculated using the equations (1) - (3) [31]:

$$A = (M_2 - M_1)/M_1 \times 100 \ (\%) \quad (1)$$

$$P_a = (M_2 - M_1)/(M_2 - M_3) \times 100 \ (\%) \quad (2)$$

$$\rho_a = M_1/(M_2 - M_3) \ (g/cm^3) \quad (3)$$

where M_1 represents the mass of the dried sample, M_2 represents the saturated mass of the sample after immersion in water, and M_3 represents the suspended mass in water of the sample.

2.5. Mechanical tests

The mechanical properties (flexural and compressive strength) of the sintered HAp samples were performed at room temperature using a Zwick universal mechanical testing machine of LFM type fitted with a 30 kN load cell. The loads were applied during the flexural and compression tests at a crosshead speed of 1 mm/min until the samples cracked. All the given values are the mean values of 3 measurements.

3. Results and discussions

All the HAp samples obtained by a hot pressure casting process exhibited a good quality and a homogeneous aspect. The selected process parameters contributed to the development of ceramic green products without defects visible by the naked eye. Thus, the cast samples were suitable for further processing and investigation. The final sizes of the samples sintered at 1150°C, 1200°C, and 1250°C for 2 hours were 10±0.05 mm in diameter and 40±0.3 mm in length. The shape of all the cast samples was preserved after sintering and the volume shrinkage was up to 3 %.

3.1. Structural characterization

Figure 1 shows the diffractograms of the HAp ceramics cast without a porogen agent and sintered at 1150°C, 1200°C, and 1250°C for 2 hours. When indexed by the ICDD PDF2 database the patterns were associated with the presence of two crystalline phases, file #01-073-4869 for $Ca_3(PO_4)_2$, and file #01-073-4869 for $Ca_5(PO_4)_3(OH)$. The elementary cell parameters, the average crystallite size, and the ratio of crystalline phases were determined by Rietveld analysis and are presented in Table 1.

The main attributed phase of $Ca_3(PO_4)_2$ is developing with temperature increase in good agreement with the literature [26, 27]. The slight variation of elementary cell parameters with the sintering temperature is due to the residual stress specific to the development of the crystalline phases with the temperature.

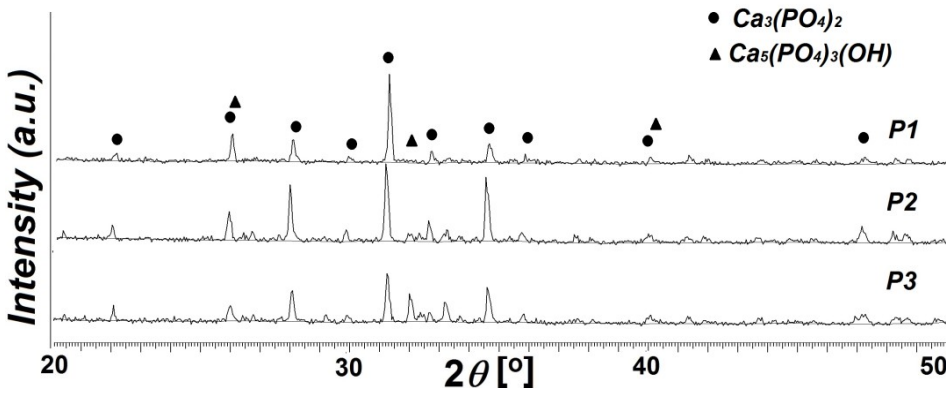

Fig. 1 - X-ray diffraction patterns of the HAp ceramic samples cast without a porogen agent and sintered at 1150°C, 1200°C, and 1250°C for 2 hours (PDF file #01-073-4869 for • $Ca_3(PO_4)_2$ and PDF file #01-073-4869 for▲ $Ca_5(PO_4)_3(OH)$) / *Diagramele de difracție de raze X a probelor ceramice HAp turnate fără agent porogen și sinterizate la 1150°C, 1200°C și 1250°C pentru 2 ore (fișier PDF #01-073-4869 pentru • $Ca_3(PO_4)_2$ și fișier PDF #01-073-4869 pentru▲ $Ca_5(PO_4)_3(OH)$).*

Table 1

Elemental cell parameters, mean crystallite size and crystal phase content for the HAp samples cast without a porogen agent and sintered in the temperature range of 1150-1250°C / *Parametrii celulei elementare, dimensiunea medie de cristalit și conținutul fazelor cristaline pentru probele de HAp turnate fără agent porogen și sinterizate în intervalul de temperatură de 1150-1250°C.*

Sample code	Sintering temperature (°C)	Crystalline phase	Crystalline structure	Weight fraction (%)	Lattice parameters (Å)		Mean crystallite size (nm)
					a	*c*	
P1	1150	$Ca_3(PO_4)_2$	hexagonal	86	10.36	37.17	132
		$Ca_5(PO_4)_3(OH)$	rhomboedral. H axes	14	9.34	6.86	133
P2	1200	$Ca_3(PO_4)_2$	hexagonal	94	10.37	37.19	149
		$Ca_5(PO_4)_3(OH)$	rhomboedral. H axes	6	9.34	6.87	98
P3	1250	$Ca_3(PO_4)_2$	hexagonal	98	10.35	37.03	165
		$Ca_5(PO_4)_3(OH)$	rhomboedral. H axes	2	9.34	6.89	75

The porogen agent does not influence the crystalline structures during the sintering process. Thus, the HAp samples cast with a porogen agent and sintered were not investigated by XRD.

3.2. Morphological characterization

Figures 2 - 4 show the SEM micrographs for the HAp samples cast without a porogen agent and sintered in the temperature range of 1150-1250°C.

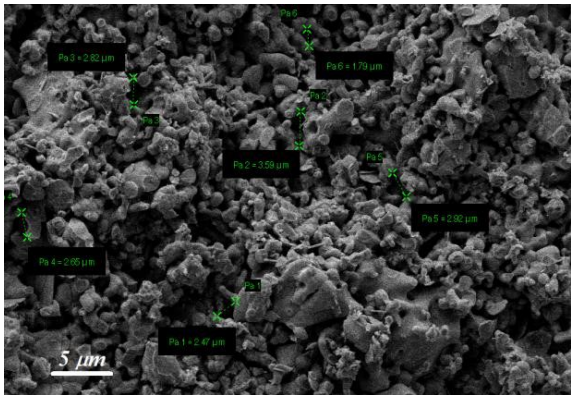

Fig. 2 - SEM micrograph of the HAp samples cast without a porogen agent and sintered at 1150°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate fără agent porogen și sinterizate la 1150°C, 5 kX.*

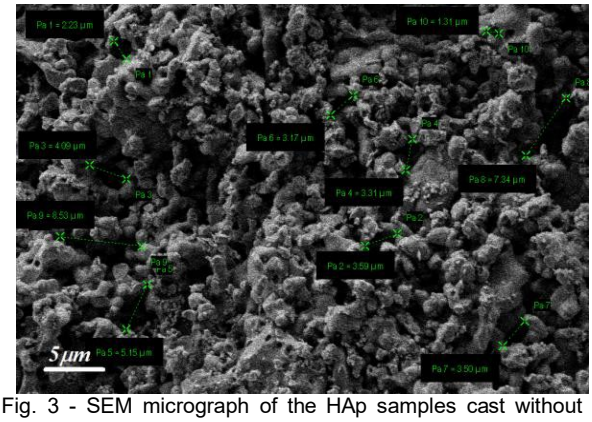

Fig. 3 - SEM micrograph of the HAp samples cast without a porogen agent and sintered at 1200°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate fără agent porogen și sinterizate la 1200°C, 5 kX.*

The microstructure of the HAp samples sintered at 1150°C (Fig. 2) shows individual granules with dimensions ranging from 750 nm to 1 μm and joined in aggregates of 2-5 μm with micropores of 1-7 μm. The HAp samples sintered at 1200°C (Fig. 3) have the appearance of a sintered ceramics with joined micron granules and a relatively closed microporosity with pores of 1.3-8.5 μm. The increase of the temperature at 1250°C (Fig. 4) allows the obtaining of well sintered ceramics, structurally homogeneous, made of agglomerates of large granules with micropores of 1-5 μm.

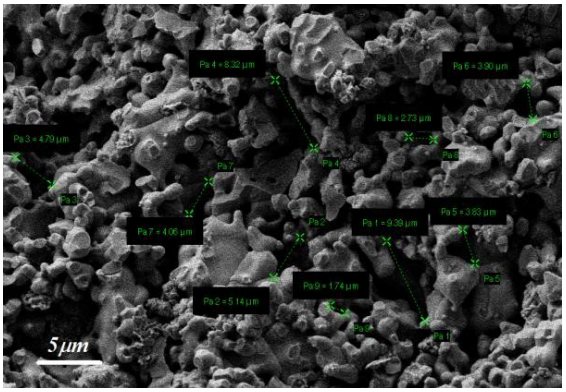

Fig. 4 - SEM micrograph of the HAp samples cast without a porogen agent and sintered at 1250°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate fără agent porogen și sinterizate la 1250°C, 5 kX.*

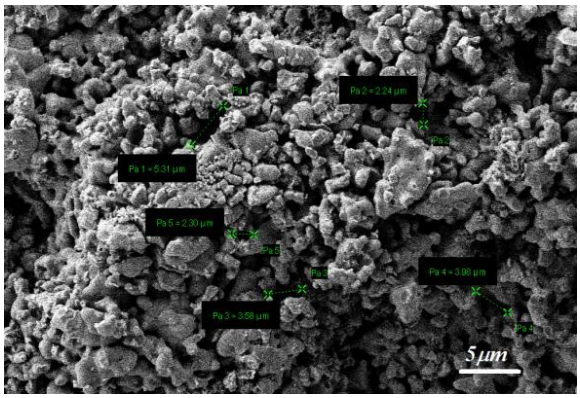

Fig. 5 - SEM micrograph of the HAp samples cast with a porogen agent (5 wt.%) and sintered at 1150°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 5% agent porogen și sinterizate la1150°C, 5 kX.*

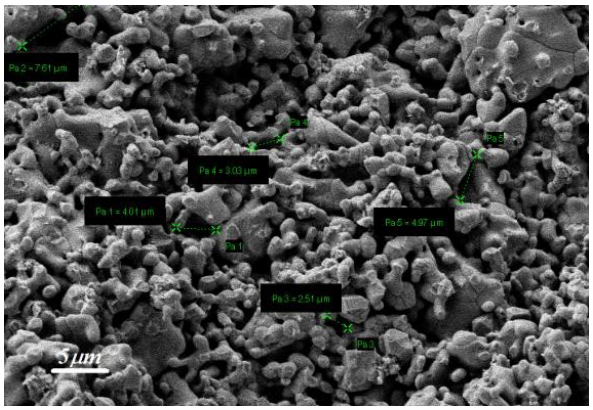

Fig. 6 - SEM micrograph of the HAp samples cast with a porogen agent (5 wt.%) and sintered at 1200°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 5% agent porogen și sinterizate la 1200°C, 5 kX.*

Figures 5-7 show SEM micrographs for the HAp samples cast with a porogen agent (5 wt.%) and sintered at 1150-1250°C.

The microstructure of the HAp samples sintered at 1150°C (Fig. 5) consists of independent granules of 1-3 µm and agglomerates with sizes up to 7 µm. The addition of the porogen agent caused the formation of individual macropores with dimensions of 101-241 µm. The increase of the

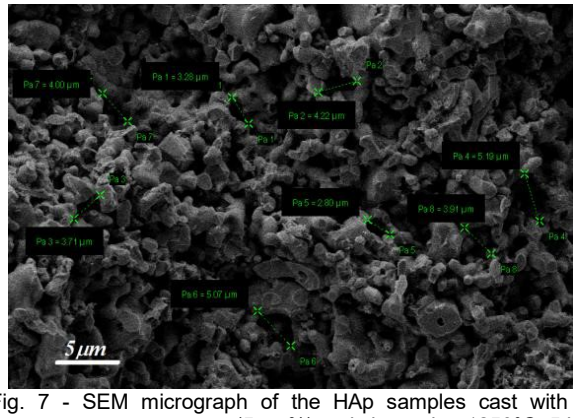

Fig. 7 - SEM micrograph of the HAp samples cast with a porogen agent (5 wt.%) and sintered at 1250°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 5% agent porogen și sinterizate la 1250°C, 5 kX.*

temperature at 1200°C (Fig. 6) led to the obtaining of sintered ceramics with a homogeneous structure composed of granules of 500-750 nm and agglomerates with dimensions up to 5 µm with micropores of 2.5-7.6 µm, constituting a partially interconnected microporosity. At the sintering temperature of 1250°C (Fig. 7) the microstructure is mainly composed of agglomerates with dimensions of 1-7 µm, slightly joined comprising a micropory of 1-5 µm, which connects macropores with dimensions of 243-384 µm. In conclusion, the addition of the Ethocel pore-forming material (particle size of 100-400 µm) in a proportion of 5 wt.% allowed the obtaining of structures with micro and macroporosity, partially interconnected.

Figures 8-10 show SEM micrographs for the HAp samples cast with a porogen agent (10 wt.%) and sintered at 1150-1250°C.

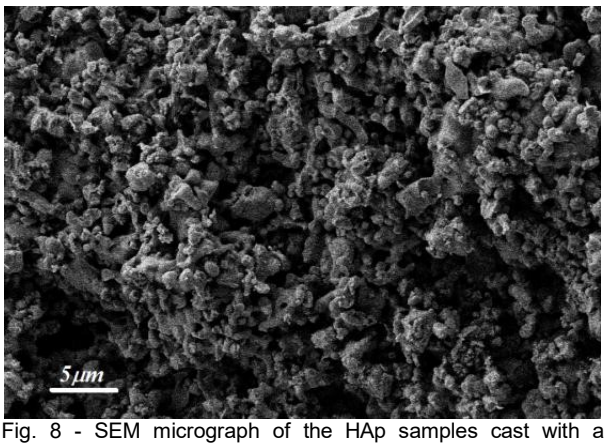

Fig. 8 - SEM micrograph of the HAp samples cast with a porogen agent (10 wt.%) and sintered at 1150°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 10% agent porogen și sinterizate la1150°C, 5 kX.*

The microstructure of the HAp samples sintered at 1150°C (Fig. 8) consists of joined granules with a size of ~ 400 nm and agglomerates of the order of microns. The structure contains micropores of 1-3 µm and macropores of 194-404 µm without the aspect of sintered ceramics.

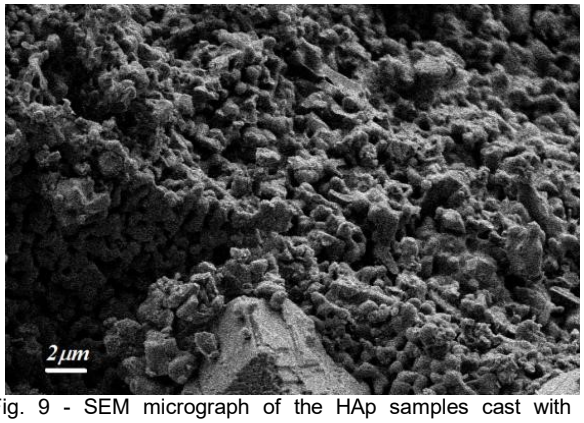

Fig. 9 - SEM micrograph of the HAp samples cast with a porogen agent (10 wt.%) and sintered at 1200°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 10% agent porogen și sinterizate la 1200°C, 5 kX.*

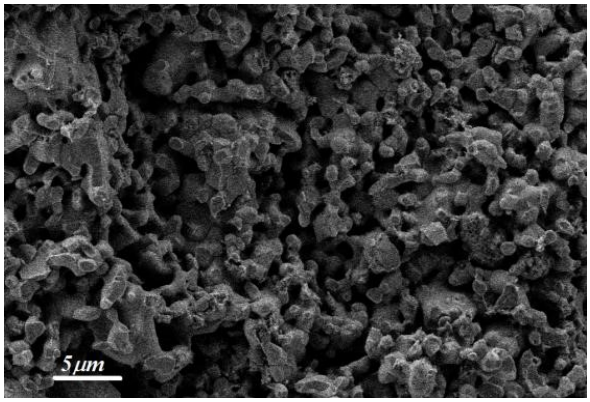

Fig. 10 - SEM micrograph of the HAp samples cast with a porogen agent (10 wt.%) and sintered at 1250°C, 5 kX / *Imagine de microscopie electronică (SEM) a probelor de HAp turnate cu 10% agent porogen și sinterizate la 1250°C, 5 kX.*

Table 2

Water absorption, apparent porosity and apparent density of the HAp samples cast without a porogen agent and sintered in the temperature range of 1150-1250°C / *Absorbția apei, porozitatea aparentă și densitatea aparentă a probelor de HAp turnate fără agent porogen și sinterizate în intervalul de temperatură de 1150-1250°C.*

Sample code	Sintering temperature (°C)	Water absorption (%)	Apparent porosity (%)	Apparent density (g/cm^3)
P1	1150	30.10	48.66	1.57
P2	1200	28.50	47.31	1.66
P3	1250	24.90	43.32	1.74

Table 3

Water absorption, apparent porosity and apparent density of the HAp samples cast with a porogen agent and sintered in the temperature range of 1150-1250°C / *Absorbția apei, porozitatea aparentă și densitatea aparentă a probelor de HAp turnate cu agent porogen și sinterizate în intervalul de temperatură de 1150-1250°C.*

Sample code	Porogen agent (wt.%)	Sintering temperature (°C)	Water absorption (%)	Apparent porosity (%)	Apparent density (g/cm^3)
P1/5	5	1150	37.19	51.69	1.39
P1/10	10	1150	44.61	57.55	1.29
P2/5	5	1200	34.01	50.67	1.49
P2/10	10	1200	39.05	56.23	1.44
P3/5	5	1250	30.26	48.12	1.59
P3/10	10	1250	34.75	52.48	1.51

By increasing the temperature at 1200°C (Fig. 9) begins the sintering process with the formation of bridges between particles with sizes of 500-650 nm and a microporosity (diameter of poors 1-2 μm) and a macroporosity (isolated macropores of 200-300 μm), respectively. At a temperature of 1250°C (Fig. 10) the ceramic samples are well sintered presenting well-developed individual granules of the order of microns, as well as large granules of 5-7 μm. The porosity consists of micropores of 1-10 μm and macropores of 200-400 μm, some of them being even joined. The obtained results are encouraging since relatively high porosity and pore size can be an important factor in the capacity of ceramic materials to achieve good biological properties.

3.3. Determination of water absorption, apparent porosity and apparent density

The values obtained from the measurements of water absorption, apparent porosity and apparent density of the HAp samples cast without and with a porogen agent and sintered in the temperature range of 1150-1250°C are presented in Table 2 and Table 3, respectively.

The results summarized in Table 2 and Table 3 indicate an increase in the apparent density, as well as a decrease of both apparent porosity and water absorption with the increase of the sintering temperature from 1150°C to 1250°C [29, 30]. In general, the addition of a porogen agent in sintered ceramics has the effect of decreasing density and mechanical strength, compared to that without a porogen agent. This finding is in agreement with our results obtained for the apparent density of the samples cast without a porogen agent and sintered at 1150-1250°C ranging between 1.57±0.01 g/cm^3 and 1.74±0.02 g/cm^3, while the apparent density for the samples cast with a porogen agent and sintered at 1150-1250°C decreased from 1.29±0.01 g/cm^3 to 1.59±0.03 g/cm^3. Accordingly, the values of the apparent porosity increased with the increase of

Table 4

Mechanical characteristics of the HAp samples cast without a porogen agent and sintered in the temperature range of 1150-1250°C *Caracteristicile mecanice ale probelor de HAp turnate fără agent porogen şi sinterizate în intervalul de temperatură de 1150-1250°C.*

Sample code	Sintering temperature (ºC)	Flexural strength (MPa)	Compression strength (MPa)
P1	1150	5.74	6.24
P2	1200	7.32	8.99
P3	1250	8.22	13.05

Table 5

Mechanical characteristics of the HAp samples cast with a porogen agent and sintered in the temperature range of 1150-1250ºC *Caracteristicile mecanice ale probelor de HAp turnate cu agent porogen şi sinterizate în intervalul de temperatură de 1150-1250°C.*

Sample code	Porogen agent (wt.%)	Sintering temperature (ºC)	Flexural strength (MPa)	Compression strength (MPa)
P1/5	5	1150	5.22	6.02
P1/10	10	1150	4.29	5.67
P2/5	5	1200	5.59	8.25
P2/10	10	1200	5.36	7.16
P3/5	5	1250	7.75	10.63
P3/10	10	1250	6.89	9.90

the content of the porogen agent (Ethocel, granulometric fraction 100-400 μm) belonging to the family of thermoplastic cellulose ethers. The HAp samples sintered at 1150°C had the highest apparent porosity of up to 57.6 %, whereas the HAp samples sintered at 1250°C yielded an apparent porosity of up to 52.5 %. These results are in agreement with the findings from the microstructure investigation and consistent with data from the literature [29, 30].

A higher porosity in the structure of ceramic biomaterials like HAp used in tissue engineering facilitates blood circulation and vascularization, as well as cell migration. Therefore, highly porous structures are more biologically beneficial for medical applications [29]. In this respect, the results obtained in our research are promising to use these ceramic materials as bone substitutes for cranioplasty but further studies are needed to assess their biological properties.

3.4. Mechanical testing

Table 4 shows the mechanical characteristics (flexural and compression strength) of the HAp samples cast without a porogen agent and sintered at 1150-1250°C.

All the sintered HAp samples that were cast without a porogen agent yielded good mechanical properties showing a flexural strength of about 5.4-8.6 MPa and compression strength of about 6-13.6 MPa. Increasing the sintering temperature from 1150°C to 1250°C led to an improvement in mechanical properties. The values of the flexural strength obtained in our study are in agreement with other literature reports. Jamadon et al. [16] developed HAp ceramics via a powder injection molding (PIM) process and found out the flexural strength of about 7.3 MPa, 12 MPa, and 17.8 MPa, for the samples sintered at temperatures of 1100°C, 1200°C, and 1300°C, respectively.

The HAp samples sintered at 1250°C revealed the best mechanical behavior, showing the highest flexural strength (8.22±0.40 MPa) and compression strength (13.05±0.62 MPa) indicating a good mechanical resistance. The results are promising since in medical applications like bone implants are required materials with good mechanical strength that will diminish the risks of bone loss or fracture or damages of the bone surface [29 - 32].

Table 5 shows the mechanical characteristics (flexural and compression strength) of the HAp samples cast with a porogen agent and sintered in the temperature range of 1150-1250°C.

Usually, the addition of a porogen agent has the effect of decreasing the mechanical strength compared to the sintered ceramics without a porogen agent. Also, an increase in the apparent porosity leads to a decrease in mechanical properties. From the values presented in Table 5 can be observed that with the increase of the sintering temperature from 1150°C to 1250°C the mechanical strength increased both in the case of the samples with a content of 5 wt.% and 10 wt.% porogen agent. The higher content of the porogen agent contributed also to a decrease in mechanical strength.

4. Conclusions

Porous HAp ceramics were successfully developed by a hot pressure casting technique of ceramic slurries made of 77 wt.% HAp powder and 23 wt.% melted paraffin and bee wax binder. HAp samples were cast at 90°C and 5 atm pressure for 10 seconds without and with the addition of 5 wt.% and 10 wt.% porogen agent. The sintering of the ceramics was performed at 1150°C, 1200°C, and 1250°C for 2 hours after drying and dewaxing of the cast green samples. The final sizes of the sintered samples were10±0.05 mm in diameter

and 40±0.3 mm in length. The microstructure and structural, physical and mechanical properties were investigated to study the effect of the sintering temperature and the addition of the porogen agent on the performance of the developed ceramics. The sintered samples exhibited an apparent density of 1.28-1.76 g/cm^3, an apparent porosity of 43-57 %, a flexural strength of 4-8.6 MPa, and a compressive strength of 5.4-13.7 MPa. The technical characteristics were influenced both by the sintering temperature and the content of the porogen agent. The properties were enhanced with the increase of the sintering temperature but the addition of the porogen agent contributed to an increase of the apparent porosity and a decrease in mechanical strength. The obtained results are within the range of the technical requirements imposed for porous ceramics used in cranioplasty. The ceramics sintered at 1250°C without and with the addition of a porogen agent revealed the best properties that recommend the developed HAp materials as promising candidates for biomedical applications as bone substitutes for cranioplasty. Nevertheless, further studies are needed to assess the biological properties.

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REFERENCES

[1] S. Morshed, Current options for determining fracture union, Advances in Medicine, 2014**, 2014, 708574**

[2] Z. Rossini, A. Franzini, I. Zaed, N. Zingaretti, F. Nicolosi, B. Zanotti, Custom-made porous hydroxyapatite cranioplasty in patients with tumor versus traumatic brain injury: A single-center case series, World Neurosurg, 2020, **138**, e922-e929.

[3] J. Brie, T. Chartier, C. Chaput, C. Delage, B. Pradeau, F. Caire, M.P. Boncoeur, J.J. Moreau, A new custom made bioceramic implant for the repair of large and complex craniofacial bone defects, Journal of Cranio-Maxillofacial Surgery, 2013, **41**(5), 403-407.

[4] J. Li, C. Gsaxner, A. Pepe, A. Morais, V. Alves, G. von Campe, J. Wallner, J. Egger, Synthetic skull bone defects for automatic patient-specifc craniofacial implant design, Scientific Data, 2021**, 8, 36.**

[5] M. Prakasam, J. Locs, K, S.-Ancane, D. Loca, A. Largeteau, L. B.-Cimdina, Fabrication, properties and applications of dense hydroxyapatite: A review, Journal of Functional Biomaterials, 2015, **6**, 1099-1140.

[6] J. Bishop, A. Palanca, M. Bellino, D. Lowenberg, Assessment of compromised fracture healing, The Journal of the American Academy of Orthopaedic Surgeons, 2012, **20**(5), 273-282.

[7] G. Gigliobianco, S. R. Regueros, N. I. Osman, J. Bissoli, A. J. Bullock, C. R. Chapple, S. MacNeil, Biomaterials for pelvic floor reconstructive surgery: How can we do better, BioMed Research International, 2015**, 2015,** 968087.

[8] P.D. Costantino, J.M. Chaplin, M.E. Wolpoe, P.J. Catalano, C. Sen, J.B. Bederson, S. Govindaraj, Applications of fast-setting hydroxyapatite cement: Cranioplasty, Otolaryngology - Head and Neck Surgery, 2000, **123**(4), 409-512.

[9] A. Das, D. Pamu, A comprehensive review on electrical properties of hydroxyapatite based ceramic composites, Materials Science & Engineering C, 2019, **101**, 539-563.

[10] Z. Bal, T. Kaito, F. Korkusuz, H. Yoshikawa, Bone regeneration with hydroxyapatite-based biomaterials, Emergent Materials, 2020, **3**, 521-544.

[11] B.K. Gu, D.J. Choi, S.J. Park, M.S. Kim, C.M. Kang, C.-H. Kim, 3-dimensional bioprinting for tissue engineering applications, Biomaterials Research, 2016, **20**, 12.

[12] G. Staffa, A. Barbanera, A. Faiola, M. Fricia, P. Limoni, R. Mottaran, B. Zanotti, R. Stefini, Custom made bioceramic implants in complex and large cranial reconstruction: A two-year follow-up, Journal of Cranio-Maxillo-Facial Surgery, 2012, **40**(3), e65-e70.

[13] P. Scolozzi, Maxillofacial reconstruction using polyether-etherketone patient specific implants by ‘‘mirroring’’ computational planning, Aesthetic Plastic Surgery, 2012, **36**, 660-665.

[14] R.M. German, Divergences in global powder injection moulding, Powder Injection Moulding International, 2008, **2**, 45-49.

[15] Z. Bruno, N. Angelo, S. Riccardo, Z. Nicola, P. Stefano, P.P. Camillo, N. Federico, M. Carlotta, Custom-made hydroxyapatite cranioplasty: Radiological and histological evidence of bone-biomaterial osteointegration in five patients, Asian Journal Neurosurgery, 2020, **15**(1), 198-203.

[16] N.H. Jamadon, N.I.A. Halid, A.B. Sulong, M.H.A. Shukor, Y. Miyashita, Evaluation of sintered hydroxyapatite (HA) via powder injection molding, Jurnal Kejuruteraan, 2020, **32**(4), 671-676.

[17] S.N.A. Aziz, M.A.A. Bakar, I.M. Hussain, Effect of single based binder palm stearin on sintered properties of hydroxyapatite scaffold, Applied Mechanics and Materials, 2015, **763**, 36-40.

[18] J. Parthasarathy, 3D modeling, custom implants and its future perspectives in craniofacial surgery, Annals of Maxillofacial Surgery, 2014, **4**(1), 9-18.

[19] M. Bohner, Design of ceramic-based cements and putties for bone graft substitution, European Cells and Materials, 2010, **20**, 1-12.

[20] A.V. Knyazev, N.G. Chernorukov, E.N. Bulanov, Apatite-structured compounds: Synthesis and high-temperature investigation, Materials Chemistry and Physics, 2012, **132**(2-3), 773-781.

[21] M.Y. Zakaria, M.I. Ramli, A.B. Sulong, N. Muhamad, M.H. Ismail, Application of sodium chloride as space holder for powder injection molding of alloy titanium hydroxyapatite composites, Journal of Materials Research and Technology, 2021, **12**, 478-486.

[22] L. Zaccaria, S.J. Tharakan, S. Altermatt, Hydroxyapatite ceramic implants for cranioplasty in children: a single-center experience, Childs Nerv Syst., 2017, **33**(2), 343-348.

[23] R. Stefini, G. Esposito, B. Zanotti, C. Iaccarino, M.M. Fontanella, F. Servadei, Use of custom made porous hydroxyapatite implants for cranioplasty: postoperative analysis of complications in 1549 patients, Surgical Neurology International, 2013, **4**, 12.

[24] D. Tălpeanu, A. Cojocaru, R.I. Zamfir (Andronic), M. Bane, S. Ciuca, Comparative tests on resistance to corrosion of some nanocomposites based on titanium hydroxyapatite, U.P.B. Sci. Bull., Series B, 2016, **78**(2), 185-193.

[25] T. Zaharescu, C. Tardei, M. Râpă, M. Iordoc, Size particle effects on the thermal stability of poly(lactic acid)/ hydroxyapatite hybrids for biodegradable package, Ceramics International, 2020, **46**(6), 7288-7297.

[26] M. Hassan, M. Akmal, H.J. Ryu, Cold sintering of as-dried nanostructured calcium hydroxyapatite without using additives, Journal of Materials Research and Technology 2021, **11**, 811-822.

[27] I. Fierascu, R. C. Fierascu, R. Somoghi, R. M. Ion, A. Moanta, S. M. Avramescu, C. M. Damian, L. M. Ditu, Tuned apatitic materials: synthesis, characterization and potential antimicrobial applications, Applied Surface Science, 2018, **438**, 127-135.

[28] L. H. Gustavsson, K. H. Adolfsson, M. Hakkarainen, Thermoplastic “all-cellulose” composites with covalently attached carbonized cellulose, Biomacromolecules, 2020, **21**(5), 1752-1761.

[29] M. Sari, P. Hening, Chotimah, I.A. Dewi, Y. Yusuf, Bioceramic hydroxyapatite-based scaffold with a porous structure using honeycomb as a natural polymeric Porogen for bone tissue engineering, Biomaterials Research, 2021, **25**, 2.

[30] D. Mao, Q. Li, N. Bai, H. Dong, D. Li, Porous stable poly (lactic acid)/ethyl cellulose/hydroxyapatite composite scaffolds prepared by a combined method for bone regeneration, Carbohydrate Polymers, 2018, **180**, 104-111.

[31] P.T. Teo, S.K. Zakaria, N. Mohd Sharif, A.A. Seman, M. Ali, A. Taib, J.J. Mohamed, M. Yusoff, A.H. Yusoff, M. Mohamad, A. Ali, M.N. Masri, Application of general full factorial statistical experimental design’s approach for the development of sustainable clay-based ceramics incorporated with malaysia’s electric arc furnace steel slag waste, Crystals, 2021, **11**(4), 442.

[32] A. Yelten-Yilmaz, S. Yilmaz, Wet chemical precipitation synthesis of hydroxyapatite (HA) powders, Ceramics International, 2018, **44**(8), 9703-971.

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