

REVIEW OF THE OFFICIAL REVIEWER
on the dissertation work by MOHAMMAD SHAMS entitled “SYNTHESIS OF
HYDROXYAPATITE NANOFIBERS FOR TARGETED DRUG DELIVERY” submitted for degree of
Philosophy Doctor by specialty 6D07113 – Nanomaterials & Nanotechnologies

N	Criteria	Criteria eligibility (it is necessary to mark one of the answer options)	Justification of the position of the official reviewer
1	The topic of the thesis (as of the date of its approval) corresponds to the development of science and/or government programs	1.1 Compliance with priority areas of science development or government programs: 3) <u>The dissertation corresponds to the priority area of the development of science, approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan (New materials based on raw substances)</u>	In spite the work was carried out at own initiative of the candidate without governmental framework, the final applied results of the work could be led to accomplish the priority area of the development of science, approved by the Higher Scientific and technical commission under the Government of the Republic of Kazakhstan, such as development of new materials based raw substances, namely substituted hydroxyapatite
2	Importance for science	<u>The work makes/does not make a significant contribution to science, and it is importance is well disclosed/not disclosed</u>	The candidate performed new approach on synthesis/design/3D printing of hydroxyapatite-based scaffolds by sonochemical method with precipitation.
3	The principle of independence	Self-reliance level: 1) <u>High;</u> 2) Medium; 3) Low; 4) No independence	The work involves obtaining hydroxyapatite-based biodegradable scaffolds and their application for bone regeneration. Hydroxyapatite and Calcium pyrophosphate nanopowders were obtained from eggshell waste, and metallic nano-silicates as resin reinforcement precursors were synthesized using the sonochemical method. In addition, a biodegradable resin was prepared in which Polylactic acid-polyurethane was used as the main matrix. Printed scaffolds' physicochemical, mechanical, in vitro, and in vivo properties were studied. All elaboration were provided by the candidate personally and were published him in several articles
4	The principle of internal unity	4.1 Justification of the relevance of the thesis: 1) <u>Justified;</u> 2) Partially justified;	The fully integral research provided by the applicant. The relevance of the research topic of the doctoral dissertation on achieving an optimal

		<p>3) Not justified.</p>	<p>infill model of Triply periodic minimal surfaces and Functionally graded lattice structures, the resin composition of 3D printed scaffolds, and the study of their physicochemical and mechanical properties is undoubtedly relevant. With scaffolds' porous structure and interconnected pore networks with adequate pore size for efficient mass-transport activities (including nourishment of cells, exchanging nutrients, oxygen, and cell migration), 3D printing of biodegradable scaffolds can be designed according to each patient's specific and individual defects in a short time with the lowest cost and side effects.</p>
		<p>4.2 The content of the thesis reflects the topic of the thesis: 1) <u>Reflects;</u> 2) <u>Partially reflects;</u> 3) Does not reflect</p>	<p>The topic of the thesis covers and reflects the content of the defended thesis. Namely, this work aims to obtain optimal Triply periodic minimal surfaces and Functionally graded lattice structures as the primary scaffold model and a biodegradable resin composition for bone regeneration in orthopedic surgery.</p>
		<p>4.3. The purpose and objectives correspond to the topic of the thesis: 1) <u>correspond;</u> 2) partially comply; 3) do not match.</p>	<p>The purpose and objectives of the defended research corresponds to the broad topic of the thesis. Namely, obtaining Hydroxyapatite and Calcium pyrophosphate from eggshells, developing optimal conditions for synthesis, selecting the optimum composition with bioactivity properties, and studying their physicochemical properties; Obtaining Nanofibrous biologically soluble scaffolds as an effective drug delivery system by electrospinning; Synthesizing biodegradable resin from Polylactic acid-polyurethane as the oligomer, and Irgacure 819 as an initiator; Synthesizing of nano-metallic silicates as precursor and reinforcement agent by sonochemical method;</p>

			<p>Achieving and developing an optimal model of Triply periodic minimal surfaces and Functionally graded lattice structures as the primary scaffold model;</p> <p>Study of the scaffolds' mechanical properties for various medical uses;</p> <p>Implanting scaffolds in dog femur bone and study of the in-vivo properties and their effect on the healing process.</p>
		<p>4.4 All sections and provisions of the thesis are logically interconnected:</p> <p>1) fully interconnected;</p> <p>2) the connection is partial;</p> <p>3) there is no connection</p>	<p>The experimental work, their results and provisions formulated upon discussion of the results show up logical interconnection all part of the defended research. The validity of the set goal follows from the current state of affairs shown in the introduction section. Reaching results and their interpretation with formulation of scientifically proven provisions the candidate shows logical and fully integral approach to finalize what he done in the conclusion part.</p>
		<p>4.5 The new solutions (principles, methods) proposed by the author are reasoned and evaluated in comparison with the known solutions:</p> <p>1) there is a critical analysis;</p> <p>2) partial analysis;</p> <p>3) the analysis does not represent one's own opinions, but quotes from other authors</p>	<p>The candidate suggests classical approach to the synthesis of new coated TPMS-based bone scaffolds. New technological approach based on The optimal condition for manufacturing hydroxyapatite and calcium pyrophosphate from eggshells. New practical results must be proven with patent</p>
5	Scientific novelty principle	<p>5.1 Are the scientific results and provisions new?</p> <p>1) completely new;</p> <p>2) partially new (25-75 % are new);</p> <p>3) not new (less than 25 % are new)</p>	<p>The scientific results and provisions are completely new due mainly to Developing several algorithms for the parametric design of Triply periodic minimal surfaces and Functionally graded lattice structures from a unit cell; Using a simple and Eco-friendly sonochemical method to synthesize nanoreinforce additives; Synthesizing a UV-cured/Reinforced biodegradable resin that can be used in standard stereolithography 3D printers; and Physico-chemical, mechanical, in-Vitro, and in-Vivo studies of printed scaffolds</p>

			<p>showed the possibility of using them as functional scaffolds for bone surgery. It is proven as well by peer-reviewed publication of the candidate</p> <ol style="list-style-type: none"> 1. Daulbaev C.B., Dmitriev T.P., Sultanov F.R., Mansurov Z.A., Aliev E.T. Obtaining Three-Dimensional Nanosize Objects on a “3D Printer + Electrospinning” Machine // Journal of Engineering Physics and Thermophysics. 2017. No 5(90). P. 1115–1118. DOI:10.1007/s10891-017-1665-z. 2. Daulbayev C., Sultanov F., Aldasheva M., Abdybekova A., Bakbolat B., Shams M., Chekiyeva A., Mansurov Z. Nanofibrous biologically soluble scaffolds as an effective drug delivery system // Comptes Rendus Chimie. 2021. No 1(24). P. 1–9. DOI:10.5802/crchim.58.
		<p>5.2 Are the dissertation conclusions new? 1) completely new; 2) partially new (25-75 % are new); 3) not new (less than 25 % are new)</p>	<p>The conclusions finalized in the thesis are completely new in the discovery of the crystalline hydroxyapatite powder obtained from an aqueous solution through chemical precipitation using a biological eggshell waste has a purity of ~95%. According to EDX analysis, the Ca/P ratio is 1.5, which is suitable for medical uses and improves the osteogenesis properties of scaffolds; polymer-based fibers by electrospinning with the addition of hydroxyapatite particles are well-qualified candidates for use as biological matrixes and drug delivery agents in tissue engineering and can reduce the convalescence period; adding the resin reinforce precursors to the matrix positively affects the mechanical properties, enhancing osteogenesis and reducing the convalescence period; and producing resin reinforce precursors by ultrasonic method led to the formation of nanomaterials with suitable size, morphology, and surface properties for medical applications.</p>
		<p>5.3 Technical, technological, economic or management</p>	<p>In opinion it would be honest to assess only effects of technological solutions</p>

		<p>solutions are new and reasonable:</p> <p>1) completely <u>new</u>;</p> <p>2) <u>partially new (25-75 % are new)</u>;</p> <p>3) not new (less than 25 % are new)</p>	<p>which is new, reasonable and industry-orientated. However it should be proven by patent. Without a patent, it is difficult to assess correctly economical and managerial effectiveness of the investigation.</p>
6	Validity of key findings	<p><u>All the main conclusions are/are not based on scientifically significant evidence or reasonably well substantiated</u></p>	<p>All the main <u>conclusions are based on scientifically significant evidence (2 independent methods at least)</u> or reasonably well substantiated and classified via publications, conference presentation.</p> <ul style="list-style-type: none"> - International Kazakh-Russian symposium “Chemical physics and nanomaterials” dedicated to the 125th anniversary of N.N.Semenov (Almaty, Kazakhstan, April 09, 2021). - VI Conference of students and young scientists “Chemical physics and nanomaterials” (Almaty, Kazakhstan, 18 March 2021). - VII Conference of students and young scientists “Chemical physics and nanomaterials” (Almaty, Kazakhstan, 18 March 2022).
7	The main provisions for the defence	<p>It is necessary to answer the following questions for each provision separately:</p> <p><u>Provision 1 - Mechanical tests</u> showed that the Triply periodic minimal surfaces and Functionally graded lattice structures have good resistance against crushing and tension forces besides improving efficient mass- transport activities and can be used as potential medical scaffolds.</p> <p>7.1 Is the provision proven?</p> <p>1) <u>proven</u>;</p> <p>2) rather proven;</p> <p>3) rather unproven;</p> <p>4) unproven.</p> <p>7.2 Is it trivial?</p> <p>1) yes;</p> <p>2) <u>no</u>.</p> <p>7.3 Is it new?</p> <p>1) <u>yes</u>;</p>	<p>Provision 1 is proved by applying the above methods. This provision is new, non-trivial, and has a wide range of applications for the manufacture of medical composite scaffolds with improved mechanical characteristics. The position was fully proven and published in the rating journal Eurasian Chemico-Technological Journal (Q4, percentile 31%).</p>

		<p>2) no. 7.4 Application level: 1) narrow; 2) average; 3) wide. 7.5 Is it proven in the article? 1) yes; 2) no.</p>	
		<p>Provision 2 - Results of different analyses confirmed that nanomagnetic resin precursors enhanced Osteogenesis. 7.1 Is the provision proven? 1) proven; 2) rather proven; 3) rather unproven; 4) unproven. 7.2 Is it trivial? 1) yes; 2) no. 7.3 Is it new? 1) yes; 2) no. 7.4 Application level: 1) narrow; 2) average; 3) wide. 7.5 Is it proven in the article? 1) yes; 2) no.</p>	<p>Provision 2 is new, non-trivial, due to the use of nanomagnetic resins as a precursor in the manufacture of the matrix, because of which the mechanical properties of the composite are improved, osteogenesis is enhanced, and the period of bone recovery is reduced. The obtained data of real mechanical tests are consistent with the simulation data and confirm the method. The results of the work were published and discussed at a conference among young scientists «Chemical physics and nanomaterials» (Almaty, Kazakhstan, March 2022).</p>
		<p>Provision 3 - Printed scaffolds coated with HA could decrease the period of convalescence compared to filing the fracture with HA powder. 7.1 Is the provision proven? 1) proven; 2) rather proven; 3) rather unproven; 4) unproven. 7.2 Is it trivial? 1) yes; 2) no. 7.3 Is it new? 1) yes; 2) no. 7.4 Application level:</p>	<p>Provision 3 is new, non-trivial, determines the influence of the morphological and structural features of HA on the process of bone restoration and healing. The position was fully proven and published in the rating journal Comptes Rendus Chimie (Q3, percentile 68 %).</p>

		<p>1) narrow; 2) average; 3) wide. 7.5 Is it proven in the article? 1) yes; 2) no.</p>	
8	<p>The principle of reliability</p> <p>Reliability of sources and information provided</p>	<p>8.1 Choice of methodology - is justified or the methodology is described in sufficient detail 1) yes; 2) no.</p>	<p>Plausible and fully described synthesis, at least 2 independent methods for substances characterization make chosen methodology justified and sufficient</p>
		<p>8.2 The results of the dissertation work were obtained using modern methods of scientific research and methods of processing and interpreting data using computer technologies: 1) yes; 2) no.</p>	<p>Most methods used in the thesis are digitalized and modern such as X-ray Diffraction, SEM, TEM, IR-spectroscopy, TGA, EDX, and VSM.</p>
		<p>8.3 Theoretical conclusions, models, identified relationships and patterns have been proven and confirmed by experimental research: 1) yes; 2) no.</p>	<p>All theoretical conclusions, identified relations and patterns, any interpretation have been made or speculated on the basis of proven and confirmed experimental data</p>
		<p>8.4 Important statements are confirmed / partially confirmed / not confirmed by references to the current and reliable scientific literature</p>	<p>All statements in the thesis are consistent with results and analysis of current research in the field of - nanotechnology and nanomaterials. All statements of the obtained results are made up on comparative analysis with literature published in reputable scientific journals.</p>
		<p>8.5 Used literature sources are sufficient / not sufficient for a literature review</p>	<p>All reliable references to the scientific literature are sufficiently enough for completed reviewing. Most of 115 articles are from the last 5 years published in peer-reviewed journals</p>
9	<p>Practical value principle</p>	<p>9.1 The thesis has theoretical value: 1) yes; 2) no.</p>	<p>The most important theoretical value based on study of the main regularities of synthesis/design/3D printing of hydroxyapatite-based scaffolds by sonochemical/precipitation method.</p>
		<p>9.2 The thesis is of practical importance and there is a high</p>	<p>The scientific results obtained in the work are aimed at solving the urgent</p>

		probability of applying the results obtained in practice: 1) <u>yes</u> ; 2) no.	scientific task of creating and researching new powders on hydroxyapatite basis.
		9.3 Are the practice suggestions new? 1) completely <u>new</u> ; 2) <u>partly new (25-75% are new)</u> ; 3) not new (less than 25% are new).	The optimal condition for manufacturing hydroxyapatite and calcium pyrophosphate from eggshells was determined, and the obtained powders must be approved via patenting.
10	The quality of writing and design	Academic writing quality: 1) high; 2) <u>average</u> ; 3) below average; 4) low.	The thesis could be assessed as average quality due mainly to some minor inaccuracies and grammar mistakes, however it keeps the work scientifically valuable

Shortcomings in the content and design of the dissertation.

1. One of the important part to apply materials for biomedical purposes is biocompatible and biodegradable performances of the materials. The applicant didn't provide any data on either biocompatibility or biodegradation of the synthesized materials. Is there any speculation on such potential performances of of the obtained scaffolds?
2. The applicant postulates that the prepared scaffolds can serve as vehicles for delivering bioactive factors to manipulate cellular processes within the scaffold microenvironment, confirming by the Fig 34, which is a picture. However, the Fig. 29 demonstrates obviously typical Fickian diffusion of the bioactive substances, and it requires additional explanation from the applicant?
3. What is a reason the applicant did not applied any results for patent, such as new either synthesized substituted hydroxyapatite, or content of the composite, or procedures for scaffold production?

Decision: I support the award of the PhD degree by specialty «6D07113 – Nanomaterials & Nanotechnologies » defended by Mohammad Shams.

The official reviewer:
Rinat M. Iskakov, PhD, Professor, Sathbayev University.

