UNIVERSITATEA POLITEHNICA din BUCURESTI

SUMMARY/REZUMAT

HABILITATION THESIS / TEZA DE ABILITARE

Laser-assisted fabrication of 2D and 3D microstructures for biomedical applications

Fabricare asistata laser de microstructuri 2D si 3D pentru aplicatii biomedicale

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<u>**Habilitation Thesis: SUMMARY**</u>

Laser-assisted fabrication of 2D and 3D microstructures for biomedical applications

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From the date of obtaining the title of PhD in Physics (year 2009) until present, I performed experimental studies on laser-assisted processing of biocompatible materials for biomedical applications. More precisely, I developed 2D and 3D structures, at micrometric scale, for controlled drug delivery and for tissue engineering applications. This habilitation thesis presents a synthesis of the results on the above mentioned topic that were disseminated in over 40 scientific articles published in prestigious international ISI journals. <u>**For 23 of these articles I am the main author.**</u> The journals where the scientific articles were published belong to Q_1 (eg Scientific Reports, Biofabrication, Applied Physics Letters, International Journal of Molecular Sciences, Applied Surface Science) and Q_2 (eg Materials, Journal of Materials Science).

The structure of the habilitation thesis comprises 5 chapters. ***Chapter I*** is dedicated to an introductory part, which briefly presents the topic addressed by each chapter, emphasizing the candidate's contributions. ***Chapter II*** and ***Chapter III*** describe the most important scientific results obtained after obtaining my PhD degree. Each of these chapters is structured as follows: the introductory part presents the state of the art for every particular topic; it is followed by the description of the experimental methods used for performing the experiments and by the presentation and interpretation of the results. At the end of each chapter, the conclusions driven from the studies are summarized. ***Chapter IV*** argues the candidate's ability to coordinate research teams, to organize and manage teaching activities, as well as the plan for evolution and development of the candidate's professional career, from academic and scientific points of view. ***Chapter V*** is dedicated to brief general conclusions.

Thus, ***Chapter II*** entitled *"Laser-assisted fabrication of microstructures for controlled drug delivery"* presents experimnetal results obtained <u>**between 2010-2017**</u>, in collaboration with the National Institute of Lasers, Plasma and Radiation Physics from Magurele. <u>**For all publication summarized in this chapter, I am main author.**</u> The motivation for approaching this topic emerged from a global need to obtain biocompatible systems, at micrometric scale, capable to deliver drugs in a controlled manner (for example, under the action of specific stimuli), to be used in different therapeutic protocols. As such, I reported the first use of Matrix Assisted Pulsed Laser Evaporation (MAPLE) technique for obtaining thin layers of polymer blends, as well as of polymers blended with anti-inflammatory drugs, which was a starting point for numerous research groups worldwide [Paun et al. Appl. Phys. Lett. 2010]. In the following years, I developed this topic through innovative use of MAPLE technique for obtaining thin layers from blends of different biocompatible polymers, for the controlled release of drugs [Paun et al. Appl. Surf. Sci 2011, Paun et al. Appl. Surf. Sci 2012, Paun et al. Appl. Phys. A 2013]. Subsequently, I started to develop 3D structures, having complex architectures, for the incorporation of anti-inflammatory drugs and controlled drugs release through electrical stimuli. More specifically, starting with 2015, I used direct laser writing by 2 photon polymerization technique (Laser Direct Writing via Two Photon Polymerization, LDW via TPP) for the fabrication of reservoirs-type micro-systems, capable of incorporating and releasing drugs in a controlled manner. More concrete, I fabricated 3D microstructures in the shape of vertical, electrically conductive, micro-tubes. These microstructures were used as micro-reservoirs for anti-inflammatory drugs and cultured with osteoblast cells. Controlled drug release by electrical stimulation of the micro-reservoirs had a positive impact on the formation of bone tissue in the cultured cells [Paun et al. Appl Surf Sci 2017].

Chapter III entitled *"Laser-assisted fabrication of microstructures for tissue engineering"* presents experimental results obtained **between 2018-2020** in collaboration with National Institute of Lasers, Plasma and Radiation Physics from Magurele and for **whose publication I am main author.** Specifically, since 2018, I used the unique advantages of direct laser writing by 2photon polymerization technique (LDW via TPP) for fabricating various 3D microstructures for tissue engineering [Paun et al. Biofabrication 2018; Paun et al. Int J Molec Sci 2018; Paun et al. Materials 2019; Paun et al. Scientific Reports 2020]. I also used LDW via TPP for producing 3D microstructures based on photopolymers with embedded magnetic nanoparticles, which accelerated the differentiation of bone-forming cells under the action of static magnetic fields. In 2018, I fabricated, by LDW via TPP technique, complex 3D structures, coated with biocompatible materials with magnetic properties and whose potential to accelerate the formation of bone tissue by exposure to static magnetic fields was validated in vitro. Starting with 2019, I fabricated, using LDW via TPP technique, superparamagnetic structures with magnetic nanoparticles incorporated in a biocompatible photopolymer. Structures' exposure to static magnetic fields induced a 200% increase in the rate of bone regeneration compared to structures that were not exposed to magnetic fields.

Chapter IV presents the *factual arguments that demonstrate my ability to coordinate research teams, to organize teaching activities and to improve teaching and research activities, mandatory aspects for obtaining the "Certificate of Competence"*. In this chapter, I also present the plans for the evolution and development of my professional career, from academic and scientific points of view. In brief, I present the plan for developing my didactic activity, which is focused on improving the quality of teaching *Physics* and *Biophysics* to the students of from Politehnica University from Bucharest, as well as several research directions for my future research activity

Chapter V contains general conclusions about the scientific relevance of the results presented in this habilitation thesis.

The five chapters are followed by the bibliographic references that I used for documentation and for explaining the experimental results, as well as the list of the scientific articles that I published as main author after finishing my PhD thesis and from which I summarized the results presented in this thesis.

Teza de Abilitare: REZUMAT

Fabricare asistata laser de microstructuri 2D si 3D pentru aplicatii biomedicale

PAUN Irina Alexandra

Bucuresti, 2021

De la data obtinerii titlului de Doctor in Fizica (2009) si pana in prezent am efectuat studii experimentale privind procesarea asistata laser a materialelor biocompatible, pentru aplicatii biomedicale. Mai precis, am dezvoltat structuri 2D si 3D, la scala micrometrica, cu aplicatii in eliberarea controlata a medicamentelor si in inginera tesuturilor. Aceasta teza de abilitare prezinta o sinteză a rezultatelor prezentate în peste 40 lucrrai științifice publicate în reviste de prestigiu din străinătate, cotate ISI, pe tematicile mai sus mentionate. **Pentru 23 dintre aceste articole candidatul are calitatea de autor principal. Revistele in care au fost publicate articolele sunt din zonele Q1 (ex. Scientific Reports, Biofabrication, Applied Physics Letters, International Journal of Molecular Sciences, Applied Surface Science) și Q2 (ex. Materials, Journal of Materials Science).**

Teza de abilitare cuprinde 5 capitole. ***Capitolul I*** este dedicat ***partii introductive***, care prezinta succint tematicile abordate in cadrul fiecarui capitol, **cu sublinierea contributiilor candidatului**. ***Capitolele II si III*** descriu cele mai importante ***rezultate stiintifice obtinute de catre candidat dupa obtinerea titlului de doctor.*** Fiecare dintre aceste capitole este structurat astfel: o parte introductivă, cu prezentarea stadiului actual al subiectului abordat, urmată de descrierea metodelor experimentale utilizate, de prezentarea si intrepretarea rezultatelor obtinute si, in final, de concluziile la care s-a ajuns in urma efectuarii studiilor. In ***Capitolul IV*** este argumentata ***capacitatea candidatului*** de a coordona echipe de cercetare, de a organiza și a gestiona activități didactice, precum si planul de evoluție și dezvoltare a carierei profesionale a candidatului, din punct de vedere academic si stiintific. ***Capitolul V*** este dedicat unor ***concluzii generale***.

Astfel, în ***Capitolul II,*** intitulat ***"Fabricarea asistata laser de microstructuri pentru eliberarea controlata a medicamentelor",*** sunt prezentate **rezultate obtinute in perioada 2010-2017** in colaborare cu Institutul National pentru Fizica Laserilor, Plasmei si Radatiei din Magurele, **pentru a caror publicare am calitatea de autor principal.** Motivatia pentru abordarea acestui subiect s-a bazat pe necesitatea construirii unor sisteme biocompatibile, la scara micrometrica, capabile sa elibereze medicamente in mod controlat (de exemplu, sub actiunea unor stimuli) si care sa poata fi utilizate in diferite scheme de tratament. In 2010, am raportat prima utilizare a tehnicii de evaporare laser pulsata asistata de o matrice (Matrix Assisted Pulsed Laser Evaporation, MAPLE) pentru obţinerea de straturi subţiri din amestecuri de polimeri, precum și din polimeri combinati cu medicamente antiinflamatoare, care a constituit un punct de pornire pentru numeroase grupuri de cercetare [Paun et al. Appl Phys Lett 2010]. În următorii ani am dezvoltat această tematica, prin utilizarea inovativă a tehnicii MAPLE pentru obținerea de microstructuri 2D sub forma unor straturi subtiri din amestecuri a diferiti polimeri biocompatibili, pentru eliberarea controlată a medicamentelor [Paun et al. Appl Surf Sci 2011, Paun et al. Appl Surf Sci 2012, Paun et al. Appl Phys A 2013]. Ulterior, am construit structuri 3D, cu arhitectura complexa, pentru incorporarea de medicamente antiinflamatoare si eliberarea controlata a acestora prin stimuli de natura electrica. In acest sens, incepand din anul 2015 am utilizat utilizat tehnica scrierii directe cu laser prin fotopolimerizare cu 2 fotoni (Laser Direct Writing via Two Photon Polymerization, LDW via TPP) pentru fabricarea unor micro-sisteme de tip *micro-rezervor*, capabile să încorporeze și să elibereze medicamente în mod controlat. Astfel, am fabricat microstructuri 3D sub forma de micro-tuburi verticale, conductive din punct de vedere electric, pe care le-am utilizat ca si micro-rezervoare pentru medicamente anti-inflamatoare si pe care au fost apoi cultivate cu celule de tip osteoblast; eliberarea medicamentelor incorporate in aceste micro-rezervoare a putut fi controlata prin stimuli electrici si a promovat formarea de țesut osos in celulele cultivate [Paun et al. Appl Surf Sci 2017].

Capitolul III, intitulat ***"Fabricarea asistata laser de microstructuri pentru ingineria tesuturilor",*** prezinta rezultate experimentale obtinute **<u>in perioada 2018-2020</u>** in colaborare cu Institutul National pentru Fizica Laserilor, Plasmei si Radatiei din Magurele si **<u>pentru a caror publicare am calitatea de autor principal</u>**. Mai precis, incepand din anul 2018, am utilizat avantajele unice ale scrierii directe cu laser prin fotopolimerizare cu 2 fotoni (LDW via TPP) pentru fabricarea de microstructuri 3D pentru ingineria țesuturilor [Paun et al. Biofabrication 2018; Paun et al. Int J Molec Sci 2018; Paun et al. Materials 2019; Paun et al Scientific Reports 2020]. Astfel, in anul 2018 am utilizat tehnica LDW via TPP pentru producerea unor microstructuri biomimetice pe baza de fotopolimeri cu nanoparticule magnetice încorporate, care au accelerat diferențierea celulelor de tip osteoblast, sub actiunea unor campuri magnetice statice. Tot in anul 2018 am fabricat, prin tehnica LDW via TPP, structuri 3D complexe, acoperite cu materiale biocompatibile cu proprietati magnetice, care au fost testate *in vitro* pentru accelerarea formarii de tesut osus prin expunere la campuri magnetice. Începand cu anul 2019 si continuand in 2020 am fabricat, utilizand tehnica LDW via TPP, structuri superparamagnetice cu nanoparticule magnetice încorporate într-un fotopolimer biocompatibil. Expunerea acestora la campuri magnetice statice a indus o creștere de 200% a ratei de regenerare osoasă în comparație cu structurile care nu au fost expuse câmpurilor magnetice.

In ***Capitolul IV*** sunt prezentate argumente factuale care demonstreaza capacitatea candidatului de a coordona echipe de cercetare, de a organiza activități didactice si de a imbunatati activitatile de predare și cercetare, ***aspecte obligatorii pentru obținerea "Atestatului de abilitare"***. De asemenea, in acest capitol sunt prezentate si planurile de evoluție și dezvoltare a carierei profesionale a candidatului, atat din punct de vedere academic, cat si stiintific. In acest sens, sunt descrise planul de dezvoltare a activitatii didactice (axat pe moduri de imbunatatire a calitatii actului de predare a materiilor *Fizica* si *Biofizica* pentru studentii Universitatii Politehnica din Bucuresti), precum si cateva direcții de cercetare propuse pentru viitor.

Capitolul V contine ***concluziile generale*** asupra relevantei stiintifice ale rezultatelor prezentate in aceasta teza de abilitare.

Cele 5 capitole de mai sus sunt urmate de referintele bibliografice utilizate pentru documentare si pentru explicarea rezultatelor experimentale, precum si de lista cu articolele publicate de candidat din care au fost extrase rezultatele prezentate in aceasta teza de abilitare.