



STATEMENT

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About a dissertation work for awarding the educational and scientific degree “Doctor of Philosophy”, field of higher education: 7. Healthcare and Sport, Professional area: 7.3. Pharmacy, Doctoral program: Pharmaceutical Technology and Biopharmacy

Author of the dissertation work: Nikolay Stanchev Zahariev

Form of the doctoral program: full-time form

Department: Pharmaceutical Sciences, Faculty of Pharmacy, Medical University - Plovdiv

Dissertation thesis: “Nanosized carriers for targeted drug delivery for antitumor therapy”

Scientific supervisor: Assoc. Prof. Bissera Pilicheva, PhD, Medical University – Plovdiv

This report is prepared in response to Order № P-1175/16.04.2024 issued by Vice Rector of Science and Research Activities of the Medical University of Plovdiv (according to Order № P-3580/05.12.2023) and the report from the first meeting of the Scientific Jury from 19.04.2024.

General introduction of the procedure and the doctoral student

The presented set of documents and materials fully meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation and is in accordance with Acquisition of Doctorate and Doctor of Science degrees at the MU - Plovdiv, Regulations of MU-Plovdiv.

Nikolay Zahariev obtained a Master's degree in Pharmacy at Medical University of Plovdiv in 2017. He has been an assistant professor in the Department of Pharmaceutical Sciences, involved in teaching of the course "Pharmaceutical Technology and Biopharmacy". By Order of the Rector of MU-Plovdiv № P-2060/17.12.2021, Zahariev was enrolled as a full-time PhD student at the Department of Pharmaceutical Sciences with a dissertation title “Nanosized carriers for targeted drug delivery for antitumor therapy” and by Order of the Vice Rector of MU-Plovdiv № P-1019/01.04.2024 he was given the right for the dissertation defense.

The doctoral student has participated in training seminars related to the acquisition of new methods of analysis - school of electron microscopy (2019), protection and welfare of experimental animals used for scientific or educational purposes (2022), as well as conducting postgraduate specialization in "Pharmaceutical technology with Biopharmacy".

Nikolay Zahariev is actively involved in both teaching and research activities of the Department, as evidenced by his participation in 5 scientific projects, 2 national scientific programs, 1 educational project, 17 national and international conferences and seminars. His high publication activity is impressive – for the last three years with his participation have been published 11 articles in journals indexed in Scopus, 3 of them are related to the subject of the dissertation.

Significance of the dissertation to science and practice

The dissertation aims to design nano-sized drug systems that deliver cytostatics to targeted areas, with improved safety and increased therapeutic effectiveness. The topic is significant for the science and the practice, given the social importance of the cancer diseases, and the undeniable therapeutic advantages of nanoparticles. In recent years, nanosystems have been one of the primary focuses of pharmaceutical technology. The development of innovative drug carriers to provide targeting of cytostatics in the tumor cells and tissues is one of the main challenges facing modern oncology related to the pursuit of limiting the manifestation of adverse drug reactions and ensuring maximum antitumor effect.

Understanding of the topic

The literature review and analysis conducted demonstrate a thorough knowledge of the challenges and complexities associated with the conventional use of cytostatics in cancer treatment, and the potential benefits of utilizing nano-sized drug delivery systems for improved therapy. The advantages of using stimuli-sensitive nanocarriers, with a focus on pH-dependent polymers, are discussed in detail as a preferred material for targeted drug release in tumor tissues or cells. The use of natural biodegradable and biotolerable polymer casein is well-justified, and various approaches for increasing drug entrapment efficiency and achieving modified drug release through protein crosslinking and/or inclusion in a polyelectrolyte complex are analyzed. The method of nano-spray drying is also extensively detailed, including its basic principles and technological factors that are essential for designing drug systems with desired characteristics. The references cited are comprehensive and include 232 literature sources.

Methodology of the dissertation

The methodology chosen for this study includes various research stages, each logically related to the next, in order to achieve the set goal. The first step involves determining the optimal conditions for the production of casein nanoparticles. The second step is to include a model drug substance in the nanoparticles. The third step is to functionalize the formulated structures by adding a second polymer - fucoidan. Statistical models of experimental design, such as the 3^2 full factorial design and $3(k p)$ partial factorial design, were used and properly applied to evaluate technological variables in nanoparticle development and to derive optimal production parameters.

To carry out this study, a wide range of modern analysis methods were utilized, including scanning and transmission electron microscopy, infrared spectroscopy, dynamic light scattering, powder X-ray diffraction, thermogravimetric and differential thermal analysis, RP-HPLC-UV analysis, differential scanning calorimetry, and fluorescence spectroscopy. The resulting drug systems were also subjected to *in vitro* dissolution tests and cytotoxicity assessment. An *ex vivo* methodology was applied to study the effect of the model drug and drug-loaded nanoparticles on the spontaneous contractile activity of smooth muscle preparations.

Characteristics and evaluation of the dissertation

The dissertation presented meets all the requirements of the Rules of MU-Plovdiv for acquiring the Doctor's degree. It contains all the main sections: Literature review, Aim and tasks, Materials and methods, Results and discussion, Conclusions, Contributions, References, and Supplementary materials. The dissertation is presented on 156 pages, illustrated with 50 figures, and 20 tables. The literature review shows excellent knowledge of literature, a good theoretical base of the doctoral student on the problems of the dissertation, and the ability to skillfully analyze scientific information. The aim of the dissertation is clearly formulated, and 8 specific and properly defined tasks have been outlined for its realization. The materials and methods used are described in detail and correctly, which guarantees accurate and reproducible results. The original results represent the most voluminous part of the dissertation - 60 pages and illustrated by 37 figures and 17 tables. The results are competently and thoroughly discussed, with skillfully reasoned conclusions. The doctoral student presents 8 comprehensive conclusions based on the results obtained. The contributions of the dissertation are mainly of a scientifically applied nature, and are correctly formulated. The most significant contribution is the design of an innovative daunorubicin-delivering nanosystems based on casein and fucoidan. Also, the studied impact of daunorubicin on the spontaneous shortening activity of smooth-muscle preparations from the corpus part of the guinea pig stomach is notable.

Assessment of the publications related to the dissertation work

The dissertation results were published in three Scopus-indexed publications, which meet the criteria for a PhD degree. It should be noted that the doctoral student have published in high-impact and top-ranked journals (Polymers: impact factor of 5.0 and Q1 ranking, and Pharmaceutics: impact factor of 5.4 and Q1 ranking). The publications have already received 14 citations in Scopus-indexed journals. Additionally, a utility model has been registered based on the developed drug systems, which is a clear indication of the relevance and significance of the work presented. The doctoral student is the first author in all three publications and in the presented six participations in international and national scientific forums, demonstrating his personal contribution to the research, analysis, and summarization of the dissertation results.

Dissertation summary

The dissertation summary presented consists of 70 pages and includes 17 tables and 41 figures. It provides an accurate and clear reflection of the findings and contributions of the dissertation, fully meeting the requirements in the Regulations for obtaining academic degrees and occupying academic positions at MU-Plovdiv.

CONCLUSION

The presented dissertation by Nikolay Zahariev entitled “Nanosized carriers for targeted drug delivery for antitumor therapy” meets all the requirements of the Law on Academic Staff Development in the Republic of Bulgaria, the Regulations on Implementation of this Law, and the Regulations of Medical University of Plovdiv.

The dissertation includes scientific and scientific-applied results, which are original contributions to the science and practice. It proves that Nikolay Zahariev has comprehensive theoretical knowledge and professional skills in the scientific specialty “Pharmaceutical Technology and Biopharmacy”, as he demonstrates qualification and skills for independent conduction of scientific research.

Considering the above stated, I confidently give my positive assessment for the conducted research, presented by the above described dissertation, abstract, achieved results and contributions, and I give my recommendation to the honourable Scientific Committee to award educational and scientific degree "Doctor" to Nikolay Stanchev Zahariev, in doctoral program " Pharmaceutical Technology and Biopharmacy", field of higher education 7. Healthcare and Sports, professional field 7.3. Pharmacy.

Заличено на основание
Чл.5 §1, б. "В" Регламент (ЕС)2016/679

14.05.2024

Reviewer:


(Assoc. Prof. Plamen Katsarov, PhD)