**PhD THESIS REVIEW**

**by Prof. Milen Ventsislavov Dimitrov, Ph.D.**

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**Department of "Pharmaceutical Technology and Biopharmacy"**

External member of **THE SCIENTIFIC JURY**, appointed according to Order No. P - № P-109-269/18.06.2025 of the Rector of the Medical University " Prof. Dr. Paraskev Stoyanov" -Varna, in the procedure for acquiring the educational-qualification degree "PhD" at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, in the field of higher education 7. "Healthcare and Sports", in the professional field 7.3. "Pharmacy" and PhD program "Pharmacology (incl. pharmacokinetics and chemotherapy)",

**On the dissertation work of:** Assist. Prof. Ivaylo Konstantinov Pehlivanov- PhD student in full-time study at the Department of Pharmacology, Toxicology and Pharmacotherapy, enrolled by order No. R-109-547/03.12.2021

**On Topic: "Self-emulsifying drug delivery systems as a method for increasing the intestinal permeability of alendronate sodium"**

Scientific supervisors: Prof. Kaloyan Georgiev, D.Sc., and Assoc. Prof. Velichka Andonova, Ph.D.

## OVERVIEW OF THE OBTAINED MATERIALS

The set of materials presented by the Assist. Prof. Ivaylo Konstantinov Pehlivanov is following Art. 69 for Regulations on the Academic Staff development at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, regulating the terms and conditions for holding academic positions-Varna/08.07.2024.

The dissertation extends over 140 pages and is well-illustrated with 33 tables and 34 figures. The bibliography is comprehensive, including 302 references. I found no shortcomings in the documentation provided by Ivaylo Pehlivanov concerning the procedure. I further declare that I have not co-authored any scientific work with the doctoral student.

## BRIEF BIOGRAPHICAL DATA AND CAREER DEVELOPMENT

Assist. Prof. Ivaylo Konstantinov Pehlivanov graduated from the 8th Secondary School "Al. S. Pushkin" - with teaching of foreign languages, Varna, in 1998. He graduated from the Medical College at the Medical University-Varna, specialty "assistant pharmacist" - professional bachelor in 2001. He graduated from the Faculty of Pharmacy at the State University of Milan of Sciences (Facolta' di Farmacia- Universita' degli Studi di Milano - Statale), Milan, Italy, specialty "Pharmacy" and a qualification degree "Master in Pharmaceutical Chemistry and Technologies" in 2009. In 2010, he successfully passed the State Exam at the Faculty of Pharmacy at the State University of Milan of

Sciences (Facolta' di Farmacia- Universita' degli Studi di Milano - Statale) for licensing for the right to practice the profession "Pharmacist", allowing entry into the professional organization.

The career development of Mag. Pharm. Ivaylo Konstantinov Pehlivanov, as an academic lecturer, started in February 2016 after winning a competition at the Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, with teaching and research work in the field of "Pharmaceutical technology and Biopharmacy". In 2020, he acquired a specialty in "Technology of Drugs with Biopharmacy" at the Faculty of Pharmacy at the Medical University of Sofia. Mag. Pharm. Ivaylo Konstantinov Pehlivanov was dismissed with the right to defense by Order R-109-269/18.06.2025.

## EVALUATION OF THE DISSERTATION

### *Relevance of the Topic*

The subject of the dissertation is highly relevant and fully consistent with the priority research areas of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. The work is multidisciplinary, focusing on pharmaceutical technology and pharmacology, including an in vivo study of the oral bioavailability of sodium alendronate (NaALD) from double self-emulsifying drug delivery systems (DSEDDS) in the urine of male Wistar rats, while also integrating approaches from pharmaceutical analysis.

The dissertation is directed towards the development of an innovative w/o/w double self-emulsifying drug delivery system with the potential to enhance the oral bioavailability of sodium alendronate.

### *Structure of the Dissertation*

**Volume and Sections**

The dissertation of Mag. Pharm. Ivaylo Konstantinov Pehlivanov consists of 140 pages and is illustrated with 34 figures and 33 tables. Its structure complies with established European and national standards. The dissertation is organized into the following main sections: Introduction – 1 page; Literature Review – 41 pages; Aims and Objectives – 2 pages; Materials and Methods – 17 pages; Results and Discussion – 40 pages; Conclusions – 1 page; Scientific Contributions – 1 page; References – 23 pages. The bibliography comprises 302 sources. In addition, appendices include records of publications in scientific journals, participation in scientific forums and projects, as well as citations related to the dissertation.

**Literature Review**

The presented literature review is logically structured, consistent, and well-argued. It provides an in-depth analysis of the oral route of drug administration, with a strong emphasis on the gastrointestinal

barriers to absorption and the mechanisms of transport. This demonstrates that the doctoral candidate possesses solid knowledge of fundamental pharmacokinetic principles.

Subsequent sections of the review appropriately present the Biopharmaceutical Classification System (BCS) and osteoporosis as a socially significant disease with high prevalence among the aging population. Of particular note is the systematic way in which the role of bisphosphonates in anti-osteoporotic therapy is substantiated. The doctoral candidate shows the ability for critical analysis by addressing both their pharmacokinetic characteristics and potential adverse drug reactions.

Special attention is devoted to sodium alendronate, a representative of BCS Class III. Despite its complex absorption profile, it is convincingly argued to be a first-line therapeutic agent in the treatment of postmenopausal and glucocorticoid-induced osteoporosis. This analysis reflects the doctoral candidate's thorough understanding of the current state of knowledge in the field.

The review also stands out for its broad coverage of drug delivery systems. Bioceramic carriers and a range of contemporary approaches to improving oral absorption and reducing gastrointestinal side effects are presented in detail, ranging from the use of absorption enhancers and "prodrug" strategies to the integration of liposomes, micelles, solid lipid nanoparticles, hydrogels, and microemulsions.

Of particular significance is the comprehensive treatment of self-emulsifying drug delivery systems. Here, the doctoral candidate demonstrates not only familiarity with their classification, composition, and mechanisms of action, but also the ability to critically analyze optimization strategies, including the use of multiple emulsions and microemulsions as well as the application of phase diagrams for formulation stabilization. This reflects the candidate's high level of theoretical preparation and orientation toward innovative scientific solutions.

Furthermore, methods for the preparation and characterization of such systems are thoroughly presented, including modern pharmacopoeial tests and in vitro models for release, permeation, and lipolysis. The review concludes logically with a synthesis of available in vivo data, reinforcing the connection between experimental developments and their practical clinical applicability.

***The literature review is comprehensive, logically consistent, and methodologically well-argued, drawing on 302 up-to-date and thematically relevant sources that accurately reflect the current state of the problem. This attests to the doctoral candidate's solid theoretical preparation and high level of academic competence.***

**Aim and Objectives**

The aim of the dissertation is precisely defined – the development of an oral double self-emulsifying drug delivery system designed to enhance the bioavailability of sodium alendronate. The tasks formulated to achieve this aim are clearly stated and aligned with the research focus of the work, thereby confirming the doctoral candidate's profound competence in this field.

**Materials and Methods**

A wide range of research methods has been mastered and applied. The doctoral candidate demonstrates skillful use of and successfully applies numerous contemporary experimental techniques, including high-performance liquid chromatography (HPLC), dynamic light scattering (DLS), UV-Vis spectrophotometry, rheological studies (viscometry), classical pharmacopoeial tests, in vitro permeation prediction (Franz diffusion cell), in vivo determination of oral bioavailability, as well as statistical methods.

**Results and Discussion**

The results are presented clearly, concisely, and are well illustrated with 34 figures and 33 tables, structured into four sections comprising a total of 23 subsections. In the initial stage, the doctoral candidate developed and validated a UV-Vis spectrophotometric method for the quantitative determination of sodium alendronate, which was validated in terms of linearity, accuracy, precision, and sensitivity. The influence of surfactants on the analytical method was also investigated, with particular attention given to the effects of polysorbate 80 and phosphates.

In the subsequent stages, the research was directed towards the formulation and optimization of a stable double self-emulsifying drug delivery system (DSEDDS) with sodium alendronate. Solubility and partition coefficients in different lipids were studied, together with the critical hydrophilic-lipophilic balance, as well as the potential for stabilizing the internal aqueous phase using phosphatidylcholine and gelatin. Pseudo-ternary phase diagrams were constructed to determine the optimal ratios of emulsifiers, and stable emulsion systems with appropriate technological characteristics were developed.

The physical and thermodynamic stability of the systems was confirmed by analytical centrifugation and the dilution method, while FTIR spectroscopy demonstrated the absence of incompatibilities between sodium alendronate and the selected excipients. Self-emulsification of the DSEDDS-NaALD occurred within approximately 70 minutes, resulting in the formation of microemulsions with a bimodal droplet size distribution. Rheological studies revealed non-Newtonian, pseudoplastic behavior, suitable for encapsulation into soft gelatin capsules.

Technological and biopharmaceutical characterization of the encapsulated DSEDDS included in vitro testing of self-emulsification, dispersibility, and permeation through dialysis and PermeaPad®

biomimetic membranes. A lag effect was observed, associated with the diffusion of sodium alendronate through the lipid layer, while the PermeaPad® membrane demonstrated a retarding effect. Nevertheless, both model systems achieved nearly complete permeation of sodium alendronate within 5–9 hours. Drug release followed the Korsmeyer–Peppas model, confirming that the process is primarily limited by erosion of the outer lipid layer.

The confirmatory in vivo study in male Wistar rats demonstrated that the formulations containing phosphatidylcholine enhanced the bioavailability of sodium alendronate, in full agreement with the results obtained from the in vitro studies.

***The doctoral candidate demonstrates a strong ability to analyze results and elucidate complex cause–and–effect relationships, which is indicative of a well-developed research mindset. The presentation and discussion of the findings are characterized by high precision, depth, and analytical rigor, clearly attesting to the candidate's excellent theoretical preparation and capacity for critical and multifaceted scientific reasoning.***

**Conclusions and Scientific Contributions**

The seven conclusions and six contributions (one of theoretical significance and five of applied character) are presented with precision and consistency, representing a natural outcome of the in-depth analysis and interpretation of the data.

**Evaluation of the Contributions of the Dissertation**

The dissertation contains clearly formulated and well-substantiated contributions, combining elements of theoretical value with a predominantly applied scientific character.

The most significant achievements and contributions of the dissertation can be summarized as follows:

- ✓ For the first time, stable double self-emulsifying drug delivery systems (DSEDDS) with sodium alendronate (7%, w/w) were developed and characterized, based on coconut oil, polysorbate 80, sorbitan monooleate, phosphatidylcholine, gelatin, and water, which upon dispersion form microemulsions.
- ✓ A UV-Vis spectrophotometric method was developed and validated, ensuring reliable quantitative determination of the active substance in a lipid matrix.
- ✓ By applying a diffusion model with a biomimetic membrane, it was demonstrated that the system provides improved permeability and predictable "in vivo" performance.
- ✓ The results obtained confirm the potential of the developed approach for industrial scale-up and subsequent integration into routine production.

**Publications and Participation in Scientific Forums Related to the Dissertation**

The results of Ivaylo Pehlivanov's dissertation are reflected in two full-text publications in English indexed in Scopus, as well as in one publication in a scientific periodical indexed in the national reference list. Evidence has been presented for three participations in scientific forums: two national conferences with international participation, where the student delivered both poster and oral presentations, and one international conference (Belgrade, Serbia), where an oral presentation was given.

The list of publications and scientific activities of the doctoral student is in full compliance with the requirements, reflecting both the application of the methodologies and the results of the original research, thereby demonstrating the dissemination of the scientific knowledge obtained in connection with the dissertation. Additionally, six citations of the publications have been recorded.

**Author's Abstract**

The author's abstract has been prepared in full compliance with the regulatory requirements, is characterized by concise presentation and appropriate length, and successfully synthesizes the content of the dissertation.

**Project Funding**

It is particularly noteworthy that part of the conducted research was carried out with the financial support of Project No. 22023, funded by the Science Fund: "Evaluation of the pharmacokinetic parameters of double self-emulsifying drug delivery systems with sodium alendronate for oral administration".

**CONCLUSION**

The dissertation on the topic: " Self-emulsifying drug delivery systems as a method for increasing the intestinal permeability of alendronate sodium", authored by Assist. Prof. Ivaylo Konstantinov Pehlivanov is up-to-date, original and meets the requirements for awarding the educational and scientific degree "PhD". The dissertation contains scientific-theoretical and scientific-applied results that represent an original contribution to science and meet the on the requirements of the of the of the Act on the Development of the Academic Staff of the Republic of Bulgaria, the Regulations for its implementation and the Regulations on the Academic Staff development at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

The dissertation demonstrates that the doctoral candidate. Assist. Prof. Mag. Pharm. Ivaylo Konstantinov Pehlivanov possesses solid theoretical knowledge and professional skills in the scientific

field of Pharmacology (including pharmacokinetics and chemotherapy), and shows the qualities and abilities required for the independent conduct of scientific research.

The submitted dissertation and the accompanying publications confirm the doctoral candidate's personal contribution and highlight his excellent knowledge of the scientific issues under investigation. The candidate has also mastered a wide range of contemporary research methods, which has enabled her to convincingly present the obtained results, skillfully analyze and interpret them, and formulate well-founded conclusions and contributions.

The submitted dissertation and the accompanying publications confirm the doctoral candidate's personal contribution and demonstrate his excellent knowledge of the scientific subject matter. The candidate has also mastered a wide range of contemporary research methods, which has enabled him to convincingly present the results obtained, skillfully analyze and interpret them, and formulate well-grounded conclusions and contributions.

In view of the above, I give my ***POSITIVE ASSESSMENT*** of the research conducted, presented in the above-reviewed dissertation, the Author's abstract, achieved results, and contributions, and I ***PROPOSE to the esteemed scientific jury to award the educational and scientific degree of 'PhD' to Assist. Prof. Mag. Pharm. Ivaylo Konstantinov Pehlivanov in the scientific specialty "Pharmacology (incl. pharmacokinetics and chemotherapy)".***

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679

Sofia,
20.08.2025

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Prof. Milen Dimitrov, PhD