OPINION

by Assoc. Prof. Viliana Eduardova Gugleva-Ruseva, PhD

Department „Pharmaceutical technologies ", Faculty of Pharmacy, Medical University „Prof. d-r Paraskev Stoyanov"– Varna, Internal member of the Scientific Jury according to Order No. R-109-269/18.06.2025 of the Rector of Medical University – Varna

Regarding: *Procedure for defending a dissertation work for the acquisition of an educational and scientific degree* ***"Doctor"*** *in the field of higher education 7. Healthcare and Sport, professional field 7.3. "Pharmacy", doctoral program "Pharmacology (incl. pharmacokinetic and chemotherapy)"*

of

Ivaylo Konstantinov Pehlivanov– full time doctoral student at the Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy at Medical University – Varna

on the topic

„Self-emulsifying drug delivery systems as a method to enhance the intestinal permeability of alendronate sodium"

scientific supervisors

Prof. Kaloyan Georgiev, PhD, DSc

Assoc. Prof. Velichka Andonova, PhD

On the basis of Order No. R-109-269/18.06.2025 of the Rector of Medical University – Varna I was elected as a member of the Scientific Jury and, on the basis of Protocol No.1/26.06.2025, I was appointed to prepare an opinion on the procedure for acquiring the educational and scientific degree "Doctor" by Ivaylo Konstantinov Pehlivanov.

The documents submitted for the competition are in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the LDASRB (RILDASRB) and the Regulations for the Development of the Academic Staff (RDAS) at MU-Varna and are formatted correctly according

to the procedure for acquiring the educational and scientific degree "Doctor" at Medical University - Varna.

Candidate biographical data

Ivaylo Konstantinov Pehlivanov was born in 1979 in Varna. In 2001 he graduated as an Assistant Pharmacist at the Medical College, MU-Varna, and in 2010 he graduated as a Master of Pharmacy at the Faculty of Pharmacy at the State University of Milan of Sciences. In the period 2010-2016, he held the position of "pharmacist, head of the "sterile dosage forms" laboratory", and since February 2016 he has been appointed as an assistant professor at the Department of "Pharmaceutical Technologies" at the Faculty of Pharmacy of the Medical University – Varna. In 2020, he acquired a specialty in "Drug Technology with Biopharmacy", and since December 2021 he has been enrolled as a full-time doctoral student in the doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" at the Department of "Pharmacology, Toxicology and Pharmacotherapy" of the Faculty of Pharmacy at MU - Varna.

Relevance of the dissertation topic

Increasing the bioavailability in oral dosage forms is a challenge, as a significant portion of new drugs belong to class II, III, or IV of the Biopharmaceutical Classification System (BCS). Their oral administration is usually associated with low bioavailability, high intra- and inter-plasma variability and lack of dose proportionality. There are various approaches to increase oral bioavailability, one of the increasingly popular is the incorporation of these molecules into lipid drug delivery systems. Alendronate sodium is among the first-line drugs used in the pharmacotherapy of osteoporosis (postmenopausal and glucocorticoid-induced). It is a class III drug of the BCS, which has low gastrointestinal absorption due to its high water solubility. Also, its oral administration is associated with the occurrence of esophagitis, as well as adverse effects on the gastrointestinal tract.

Based on the above, I believe that the presented dissertation work addresses a current and significant topic related to the possibility of developing an innovative dosage form (self-emulsifying drug delivery systems) designed to increase the intestinal permeability of alendronate sodium.

Characteristics and evaluation of the dissertation work

The dissertation of Ivaylo Pehlivanov is very well structured and has been prepared in accordance with the requirements for acquiring the educational and scientific degree "Doctor". The dissertation contains a total of 140 pages divided into the following mandatory sections: Introduction (1 p.), Literature review (42 p.), Aim and tasks (2 p.), Materials and methods (18 p.), Results and discussion (41 p.), Conclusions (1 p.), Contributions (1 p.), References (24 p.), List of scientific publications and participations related to the dissertation work (1 p.). The dissertation is illustrated with 34 figures and 33 tables. The literary sources used are a total of 302, of which only 1 is in Bulgarian.

In the ***literature review***, the doctoral student has made a detailed analysis of the oral route of administration of drugs, as well as the approaches to increase oral absorption and limit the

undesirable gastrointestinal effects of sodium alendronate. A general overview of the disease osteoporosis and the therapy with bisphosphonates has been made. The composition, methods for preparation and characterization of self-emulsifying drug delivery systems are critically analyzed and pharmacopoeial control tests are reported. The doctoral student's ability to analyze and summarize literature data determines the precise formulation of the ***aim*** of the dissertation work - to prepare a W/O/W self double-emulsifying drug delivery system (SDEDDS) that enhances the oral bioavailability of alendronate sodium. The ***tasks*** set for its implementation are precisely formulated and adequately reflect the problem set in the topic of the dissertation.

The ***materials and methods*** are appropriately selected according to the purpose of the study and the implementation of the tasks set. The experimental work performed is presented in detail. For the realization of the dissertation work, numerous studies have been conducted - a UV-Vis spectrophotometric method for the quantitative determination of sodium alendronate in the models has been developed and validated, model formulations of double self-emulsifying drug delivery systems loaded with sodium alendronate were prepared, and their thermodynamic stability, self-emulsification time, droplet size after dispersion, and rheological characteristics were evaluated. Pharmacopoeial tests were conducted to control hard gelatin capsules with the included self-emulsifying drug delivery systems and the oral bioavailability of alendronate sodium from the developed carriers was studied by determining the amount of drug excreted in the urine of male white Wistar rats.

The ***results and discussion*** are well structured and follow the set tasks, with all results of the conducted research being thoroughly analyzed and discussed. The obtained results are illustrated with 27 figures and 19 tables, included sequentially in 4 subsections. The consistency in the doctoral student's work is impressive - from optimizing the composition of the dual self-emulsifying drug delivery system with sodium alendronate and its subsequent incorporation into hard gelatin capsules and their technological and biopharmaceutical characterization, to the *in vivo* studies conducted on Wistar rats, which are a natural conclusion to the developed dissertation work. The personal participation of the doctoral student in conducting the experimental research and analyzing the results is beyond doubt.

As a result of the conducted experiments, well-defined ***conclusions*** have been formulated that reflect the essence of the work. The ***contributions*** of the dissertation work are correctly summarized and are divided into those of a scientific-theoretical and scientific-applied nature. The most significant contributions could be summarized as follows:

- For the first time, chemically, physically, and thermodynamically stable SDEDDS with sodium alendronate (7% w/w) have been formulated, based on coconut oil, polysorbate 80, sorbitan monooleate, phosphatidylcholine, gelatin, and water, which self-emulsify in aqueous medium (0.1N HCl) into microemulsions.
- The application of a UV-Vis spectrophotometric method for quantitative determination of sodium alendronate incorporated in lipid-based drug delivery systems has been validated through complex formation with Fe^{3+}.
- The diffusion model with a biomimetic membrane for investigating sodium alendronate permeation from SDEDDS is suitable for predicting the system's in vivo behavior.

- For the first time, an approach has been developed for incorporating sodium alendronate into SDEDDS with enhanced drug permeability across biological membranes.
- The developed approach for incorporating sodium alendronate into SDEDDS with improved drug permeability across biological membranes is suitable for scaling under industrial conditions.

Summary of the dissertation work

The summary of the dissertation work is prepared in accordance with the requirements of the regulations, with an adequate volume (64 pages) and adequately summarizes the content of the dissertation.

Publications and participation in scientific forums related to the dissertation work

The results of the dissertation work of Ivaylo Pehlivanov are presented in 3 full-text publications, two of which in English in journals indexed in Scopus – Journal of IMAB (SJP 0.115) and Proceedings of science (SJP 0.115) and one in Bulgarian in a journal indexed in the national reference list – Varna Medical Forum. Three participations in scientific forums on the topic of the dissertation are reported, 2 in Bulgaria and 1 abroad (Belgrade, Serbia).

Project funding

I highly appreciate that part of the research was funded through a project under the Science Fund No. 22023 "Evaluation of pharmacokinetic parameters of double self-emulsifying drug delivery systems with alendronate sodium for oral administration" of the Medical University - Varna.

Conclusion

The dissertation work of Ivaylo Pehlivanov " Self-emulsifying drug delivery systems as a method to enhance the intestinal permeability of alendronate sodium " contains original results contributing to the optimization of drug delivery of sodium alendronate and fully complies with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations on the Development of Academic Staff of the Medical University - Varna. The dissertation work of Ivaylo Pehlivanov shows that the doctoral student has mastered a wide range of research methods and is able to correctly analyze the obtained results.

Based on the above, I give my **POSITIVE ASSESMENT** of the dissertation work and propose to the esteemed members of the Scientific Jury to vote **FOR** the award of the educational and scientific degree **"Doctor"** in the field of higher education 7. Health and Sports, professional field 7.3 Pharmacy, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" to Ivaylo Konstantinov Pehlivanov.

05.08.2025

Varna, Bulgaria

Prepared

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