OPINION

by Assoc. Prof. Maya Petrova Radeva-Ilieva, MScPharm, PhD

Head of Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy, Medical University "Prof. Dr. Paraskev Stoyanov" – 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. pharmacokinetics and chemotherapy)"

of

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

on the topic

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

scientific supervisors

Prof. Kaloyan Dobrinov Georgiev, MScPharm, PhD, DSc

Assoc. Prof. Velichka Yordanova Andonova, MScPharm, PhD

On the basis of Order No. P-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 present opinion is prepared in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), as well as the Regulations for the Implementation of the LDASRB (RILDASRB) and the Regulations for the Development of the Academic Staff (RDAS) at MU – Varna. The documents submitted by the candidate meet the specified requirements and are precisely prepared and arranged.

I declare that I have no joint scientific works with the doctoral student.

Biographical data of the candidate

Ivaylo Konstantinov Pehlivanov was born in 1979 in Varna. In 1998, he graduated from the Foreign language school "Al. S. Pushkin" in Varna. In 2001, he completed his study in the specialty "assistant pharmacist " in the Medical College at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. In the period 2001-2009, he studied in the specialty "pharmacy" in the Faculty of Pharmacy at the University of Milan (Facolta' di Farmacia- Universita' degli Studi di Milano - Statale), Italy, and in 2010 he successfully passed the State Exam for acquiring the professional qualification "pharmacist". In the period 2010-2016, he held the position of "pharmacist, head of the laboratory "sterile dosage forms" at the pharmaceutical factory FARMACIA DOTT. METALLA SNC in Milan, Italy. Since 2016, he has been appointed as an assistant professor in the Department of Pharmaceutical Technologies at the Faculty of Pharmacy of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. In 2020, he acquired a specialty in "Drug Technology with Biopharmacy" at the Medical University-Sofia. In 2021, he was 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

The oral route of administration is the preferred route of drug administration for chronic diseases. A number of factors influence the pharmacokinetics of orally administered drugs, but the extent of absorption is one of the main factors determining systemic bioavailability. In recent decades, pharmacy has undergone extremely rapid development in terms of dosage form technology, which has increased the possibilities for oral administration of drugs with low oral bioavailability. By incorporation of the drug into a suitable dosage form, it is possible not only to increase the extent of absorption in the gastrointestinal tract and, accordingly, systemic bioavailability, but also to reduce the severity of certain adverse drug reactions. This is of particular importance in the therapy of certain diseases, such as osteoporosis. One of the main groups of drugs used in the treatment of osteoporosis are the so-called bisphosphonates, which are very poorly absorbed in the gastrointestinal tract and have very low oral bioavailability (< 1%). At the same time, bisphosphonates have specific adverse effects on the mucous membrane of the digestive system, as they are acidic in nature. Therefore, the choice of an appropriate dosage form for oral administration is of great importance for drugs from the bisphosphonate group.

Based on the above, I believe that the presented dissertation work addresses a current and significant topic related to the development of an innovative dosage form that aims to increase the

intestinal absorption and, accordingly, the systemic bioavailability of sodium alendronate - a drug from the bisphosphonate group used in the treatment of osteoporosis.

Structure of the dissertation work

The dissertation work of Ivaylo Pehlivanov is well structured and has been prepared in accordance with the requirements for obtaining the educational and scientific degree "Doctor". The dissertation work contains a total of 140 pages, divided into the following mandatory sections:

I. Introduction – 1 p.;
II. Literature review – 42 p.;
III. Aim and tasks – 2 p.;
IV. Materials and methods – 18 p.;
V. Results and discussion – 41 p.;
VI. Conclusions – 1 p.;
VII. Scientific contributions – 1 p.;
VIII. Bibliography – 24 p.;
IX. List of scientific publications related to the dissertation work – 1 p.

The dissertation is illustrated with 33 figures and 33 tables. The cited literary sources are a total of 301, of which only 1 is in Bulgarian.

The literature review is systematically presented and contains a sufficient volume of scientific information. It is divided into several parts, which sequentially examine: the oral route of administration of drugs and in particular the mechanisms of transmembrane transport; osteoporosis; bisphosphonates, their pharmacokinetics and adverse drug reactions; as well as self-emulsifying drug delivery systems. At the end of the section, the doctoral student presented the conclusions from the prepared literature review, which are fundamental for the formulation of the goal. The presentation of the selected scientific data shows a very good knowledge of the subject.

The aim and tasks of the present dissertation work are logically related to the prepared literature review. **The aim** of the dissertation is precisely and clearly formulated and is focused on the development of a double self-emulsifying drug delivery system (w/b/w), providing increased bioavailability of alendronate sodium upon oral administration. **The tasks** are 4 in total and arise from the set purpose. They are precisely formulated and justified from the point of view of achieving the goal.

The materials and methods used are appropriately selected with regard to the tasks set and their implementation. The substances, reagents and equipment used are described in detail. Numerous studies have been conducted for the realization of the dissertation work: UV-VIS spectrophotometric analysis for quantitative determination of sodium alendronate, study of the

solubility of sodium alendronate, preparation and detailed characterization of self-emulsifying drug delivery systems loaded with sodium alendronate, *in vivo* study to assess the oral bioavailability of the prepared self-emulsifying drug delivery systems loaded with sodium alendronate in rats, statistical analysis of the obtained results. It's impressive that a wide variety of methods in different scientific fields are used, which shows the high scientific value of the present dissertation work. The experimental work performed is presented in detail.

The results and discussion are combined into one section. They are well structured and follow the tasks set, with each presented result followed by a discussion on its significance and interpretation. It is very impressive that every statement or assumption is supported and substantiated with scientific information. The results are accompanied by numerous figures and tables. I believe that the results obtained are original and reliable, supported by sufficient scientific data. The strict consistency shown in the doctoral student's work is impressive - from the development of the dosage form containing alendronate sodium and the subsequent full characterization, to conducting an *in vivo* study to assess its impact on the systemic bioavailability of the drug after oral administration.

The formulated **conclusions** originate from the obtained results and have a practical focus.

The scientific contributions of the dissertation work are well formulated. They are divided into those of a scientific-theoretical and scientific-applied nature and objectively reflect the scientific contribution of the developed dissertation work.

Summary of the dissertation work

The summary of the dissertation work contains a total of 64 pages. It is structured according to the requirements and presents important figures and tables.

The candidate's scientific activity related to the dissertation work

Three publications in scientific journals are presented, in which the doctoral student is the first author. Two of the articles was published in international journals indexed in Scopus, which is indisputable evidence of the high scientific value of the research conducted and the results obtained. The doctoral student presents three participations in scientific conferences related to the topic of the dissertation work – 2 in national forums and 1 in an international one (Belgrade, Serbia). In addition, the doctoral student participates in 4 scientific research projects, 1 of which is related to the topic of the dissertation work.

CONCLUSION

The dissertation work of Ivaylo Konstantinov Pehlivanov on the topic "Self-emulsifying drug delivery systems as a method to enhance the intestinal permeability of alendronate sodium"

fully complies with the requirements of LDASRB, RILDASRB and RDAS of MU-Varna. The dissertation work is dedicated to a current topic related to the role of the dosage form in increasing the oral bioavailability of drugs.

The present dissertation work demonstrates that Ivaylo Pehlivanov possesses in-depth theoretical knowledge and practical experience in the field of pharmaceutical technologies and pharmacology. Many and diverse methods were used for the experimental work, as a result of which significant results were obtained, which represent an original contribution to pharmaceutical science and practice. The doctoral student demonstrates qualities and abilities for independent research.

Based on the above, I give my **POSITIVE ASSESSMENT** of the present dissertation work and propose to the esteemed Scientific Jury to award the educational and scientific degree **"Doctor"** in the field of higher education 7. Health and Sport, professional field 7.3. Pharmacy, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" to **IVAYLO KONSTANTINOV PEHLIVANOV**.

20.08.2025
Varna

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

(Assoc. Prof. Maya Radeva-Ilieva, PhD)