

## **OPINION**

**by Assoc. Prof. Bissera Pilicheva, PhD**

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**Member of the Scientific Jury according to Order RD-38-615/22.12.2020 of the  
Rector of Sofia University “St. Kliment Ohridski”**

**Subject:** Procedure for defense of a dissertation for awarding the educational and scientific degree "Doctor of philosophy" in professional field 7.3 Pharmacy, doctoral program in Technology of dosage forms and biopharmacy" of the doctoral student **Zahari Penkov Vinarov** entitled "Enhancing the solubility of hydrophobic drugs by solubilization in micellar surfactant solutions"

### **General presentation of the doctoral student**

Zahari Vinarov obtained a master's degree in Pharmacy at the Medical University - Sofia in 2009. In 2008 he was appointed at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kliment Ohridski" at the Department of Engineering Chemistry and Pharmaceutical Engineering, where he has held the positions of researcher, assistant professor and chief assistant professor. He is involved in teaching of the courses "Technology of Dosage Forms and Biopharmacy", "Dispersions in Pharmaceutical Technologies" and "Chemical Kinetics". In 2014 he was awarded the educational and scientific degree "Doctor of Chemistry" from Sofia University "St. Kliment Ohridski" with a thesis entitled "In vitro studies of triglyceride lipolysis in the gastrointestinal tract". In 2019 he joined the Department of Pharmaceutical and Pharmacological Sciences of the Catholic University of Leuven (KU Leuven), Belgium, where he works as a postdoctoral fellow in the field of drug delivery.

Zahari Vinarov has authored 16 scientific publications in international journals with impact factor, he is a member of international scientific organizations (AAPS, EUFEPS) and editorial boards of reputable publishers (MDPI, Wiley). He is a participant in many research projects with national and foreign funding. He is fluent in English, Russian and French.

## **Topicality of the problem**

The dissertation examines the problem with aqueous solubility of hydrophobic drugs and the methods for its increase, with regard to the selection of optimal dosage form and route of administration, focusing on the opportunities offered by micellar solubilization. From a biopharmaceutical aspect, this is a topical issue affecting many drugs whose oral delivery is hindered due to their low solubility.

## **General presentation and structure of the dissertation**

The dissertation is structured according to the established standards. It contains 77 pages and is illustrated with 33 figures and 4 tables. The bibliography includes 110 literary sources by foreign authors.

The **introductory part** well justifies the topicality of the problem. The literary review to the dissertation is detailed and gives an idea of the in-depth knowledge of the doctoral student on the problem, as well as of his capacity for interpretation of data published in the literature. Biopharmaceutical aspects of oral administration of drugs are considered, in-depth analysis of solubility and dissolution rate is presented, classical methods for enhancing solubility and dissolution rate are described, extensive review of surfactant properties and their solutions is presented, solubilization of drugs in surfactant solutions is considered. An in-depth analysis of the relationship between the molecular structure of the surfactant and the type of the drug is made, and its effect on the solubilization process is studied. The missing elements for elucidating the molecular mechanisms of the process are outlined.

The **aim of the work** is clearly formulated: to study the influence of the molecular structure of surfactants and drugs on the solubilization capacity of micelles, resp. on the solubility of drugs. To achieve this goal, three tasks have been formulated. Sophisticated analytical methods have been used, which are a prerequisite for high reliability of the obtained results.

The **results** are considered in several aspects: a study of the solubility of progesterone as a function of the surfactant type was performed and a very strong dependence on its chemical structure was found. Substances of different classes were compared and the most substantial effect on the solubility of progesterone by anionic surfactants was found. The relationship between the chemical

structure of the surfactant and the solubilization capacity was studied. The hypothesis of ion-dipole interactions between the hydrophilic head of the surfactant and progesterone as a factor of key importance for the solubilization capacity of the micelles for this drug has been confirmed. The effect of the hydrophobic tail length of the surfactant on the solubilization capacity for progesterone was also studied and it was found that the increase of the hydrophobic tail length leads to a linear increase of the solubilization capacity for all studied surfactant types. A similar study for danazol and fenofibrate was presented, and the results were compared with those for progesterone.

Based on the obtained results, the doctoral student has made four **conclusions**, which are comprehensive and logically follow the goal and the formulated tasks.

The **contributions** of the dissertation are correctly formulated and are mainly of a scientifically applied nature. The most significant contribution is the compilation of a database on the solubilization capacity of various surfactants, which can be used in defining the solubilization of drugs in physiologically based pharmacokinetic models.

### **Evaluation of the publications on the dissertation**

The doctoral student has presented 2 scientific publications and 9 participations in scientific forums related to the dissertation. The publications are in refereed scientific journals with impact factor (Web of science), which fall into the second quartile (Q2) of the publications in the field. The total number of points according to the Minimum National Requirements by group of indicators G (according to Tables 1 and 2 of Scientific field 7. Health and Sports in the Annex 1a, Art. 1 of the Regulations for the implementation of the Law on the development of the academic staff in the Republic of Bulgaria) is 32 points at minimum number of points according to the national requirements - 30. In both presented publications Zahari Vinarov is the first author, which testifies that the work presented by the doctoral student is his personal merit. In addition, the author has presented 6 other publications related to the topic of the dissertation, all of which are in international journals with an impact factor (Web of science). There are 74 citations (according to SCOPUS, without auto-citations) of the author's scientific works.

The author's abstract is prepared according to the requirements, in sufficient volume, and adequately reflects the main results of the dissertation.

## Conclusion

The dissertation is a completed scientific work meeting the minimum requirements of the Law for development of the academic staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations of Sofia University and shows that the doctoral student has in-depth knowledge in the field, has mastered various methods and techniques and demonstrates skills for independent research .

In view of the above, I confidently give my **positive assessment** and **I propose to the Scientific Jury to award Zahari Penkov Vinarov the educational and scientific degree "Doctor" in the scientific specialty "Technology of Dosage Forms and Biopharmacy"**.

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