REVIEW

on

a dissertation for awarding the educational and scientific degree "DOCTOR" in Professional field 7.3 Pharmacy and Doctoral program "Technology of drug dosage forms and biopharmacy"

Topic of the dissertation: "*Improving the solubility of hydrophobic drugs by solubilization in surfactant micelles*"

Author: M.Sci. Zahari Penkov Vinarov - PhD student in independent training

Reviewer: Prof. Denitsa Momekova, Ph.D. - Faculty of Pharmacy, Medical University of Sofia

This Peer Review is prepared in response to Order № РД-36-615 of 22.12.2020 issued by the Rector of Sofia University "St. Kliment Ohridski". The Review is in compliance with the law of Development of Academic Staff in the Republic of Bulgaria Act (DASRB), the General regulation on its implementation and the Institutional regulations for the application of the aforementioned law at Sofia University "St. Kliment Ohridski".

Materials on the procedure:

The dissertation was discussed, approved and scheduled for defense at a meeting of the extended Department Council held on December 11, 2020. All necessary documents are submitted in accordance with the requirements of DASRB and the regulations for its implementation.

Professional development of the doctoral student:

Zahari Vinarov graduated from the Faculty of Pharmacy at the Medical University of Sofia in 2009. During the period 2008-2011 he worked as a researcher in the Department of Engineering Chemistry and Pharmaceutical Engineering at the Faculty of Chemistry and Pharmacy at Sofia University "St. Kliment Ohridski ". In 2014 he was appointed as an assistant professor to the same department, and since 2016 he has been a chief assistant professor. In 2014, after successfully defending his dissertation, he received the educational and scientific degree "Doctor" in the professional field 4.2 Chemical Sciences. Since 2019 Zahari Vinarov has been a post-doctoral student in the Department of Pharmaceutical and Pharmacological Sciences at the KU Leuven, Belgium.

Characteristics and evaluation of the dissertation:

The dissertation is written on 77 pages and includes six main sections: Introduction, Bibliographic review, Objective and tasks (Chapter 1); Materials and methods used (Chapter 2); Results and discussion (chapters 3 and 4); Conclusions, Contributions and List of cited references. The bibliography includes 110 sources, almost half of which are from the last 10 years. The dissertation is illustrated with 33 figures and 4 tables, in which the research results are presented correctly and in a very good way.

Relevance and significance of the dissertation

The aqueous solubility of drugs is a key factor for their bioavailability, especially when administered orally. On the other hand, the rapid development of high-throughput technologies and as a result the elucidation of the molecular mechanisms of a number of diseases have led to the synthesis of new molecules as potential drug candidates. Given the intracellular localization of their therapeutic targets, most of these new candidates are characterized by low water solubility and the associated low bioavailability, which makes it difficult to fulfill their clinical potential. In this regard, one of the biggest challenges that the modern technological science is facing is the formulation of water-insoluble drugs in suitable oral dosage forms. A state-of-the-art approach to increase the aqueous solubility of drugs is the micellar solubilization. Surfactants are known to play an important role in many processes of interest to both fundamental and applied science. An important property of surfactants is their ability to form supramolecular aggregates of colloidal size in aqueous solution above a certain concentration - these so called micelles can solubilize sparingly soluble substances in water. Although micellar solubilization is a commonly used approach, the mechanisms that determine and influence the degree and effectiveness of drug dissolution in micelles have not yet been fully elucidated. In this regard, the topic of the dissertation is relevant and scientifically significant and falls into the modern, rapidly evolving field of optimization of oral drug delivery.

To solve these problems, the doctoral student very correctly, on the basis of the indisputable advantages of micellar solubilization as a method of increasing aqueous solubility, focuses on in-depth study of the relationship between the molecular structure of surfactants and drugs and solubilization capacity of micelles.

Assessment of the scientific and research accomplishments and contributions of the candidate:

In the literature review, the doctoral student has made a detailed analysis of the biopharmaceutical aspects of oral drug delivery, as well as the approaches to increase the rate and degree of drug dissolution. The physicochemical properties of the surfactants as well as the micellar solubilization process are discussed in detail in

separate subsections. A critical evaluation of the literature data on the solubilization of drugs in micell-containing surfactant solutions was made. I highly appreciate the critical review of the available literature on the subject made by the candidate.

The candidate's ability to analyze the published data and the conclusions he made in several places in the review logically lead to the precise and clear formulation of the aim of the dissertation, and the tasks related to its implementation are detailed and adequately reflect the problem in the dissertation topic.

Chapter 2 of the dissertation describes in details the materials and methods used in the experimental work. The wide range of methods used for characterization of the drugs solubilized in the micelles, as well as the methods for the physicochemical characterization of the obtained micelles is impressive. The methods are adequately selected, modern, precisely described and guarantee the implementation of the tasks at a high scientific level.

Undoubtedly, the most important and interesting part of the dissertation is the presentation of own results, which can be summarized in two directions:

- ✓ Detailed study of the influence of the surfactant structure (type of hydrophilic head and length of the hydrophobic tail) on the solubilization of the three model drugs.
- ✓ Evaluation of the influence of the chemical structure and polarity of the drug substance on the solubilization capacity of surfactants.

A significant contribution of the candidate in the realization of the aim of the dissertation is the precise selection of the solubilizing agents. In this research, the candidate studied a series of 20 surfactants with different hydrophobic tail lengths and different as type and charge hydrophilic heads in terms of their solubilization capacity of three hydrophobic model substances: progesterone, danazol and fenofibrate.

The evaluation of a series of surfactants (with structurally different hydrophilic heads - anionic, cationic and nonionic) with the same length of the hydrophobic tail allows a clear determination of the role of the polar head of the surfactant in the solubilization of the studied substances. It has been convincingly proven that the type and hydrophilic head of surfactants play a decisive role in the solubilization of progesterone and danazol. These two substances have been found to solubilize much more efficiently in ionic surfactant micelles than in nonionic surfactants.

The main contribution of the candidate in this direction can be considered the hypothesis formulated on the basis of experimental data, which has subsequently convincingly proven that the solubilization of progesterone and danazol is a result of

electrostatic interactions of the ion-dipole type with ionic surfactants. The locus of solubilization of progersterone in the palisade layer of micelles has also been unequivocally proven. With respect to fenofibrate, the higher solubilizing efficacy of nonionic surfactants has been found, and the locus of solubilization is the hydrophobic nucleus of the micelles.

At the next stage, the doctoral student thoroughly analyzed the influence of the aliphatic tail length of surfactants on their solubilizing capacity, and for each type of hydrophilic heads homologous rows of surfactants with different hydrophobic tail lengths were studied. The obtained results show that regardless of the charge and the type of the hydrophilic head of the surfactant, the solubilization of the model hydrophobic substances increases with increasing length of the hydrophobic chain.

In my opinion, the main contributions of the dissertation are the clarification of the relationship between the structure of drugs and surfactants and the effectiveness of solubilization, which in turn is a prerequisite for optimal choice of solubilizing agent in the development of drug dosage forms. In addition, the type of specific intermolecular interactions between surfactants and drug molecules as well as their role in the solubilization process are clarified. The last section of the dissertation contains four well-defined conclusions, fully corresponding to the essence of the work, which I fully accept. The contributions are also correctly summarized and significant.

Questions, recommendations and remarks:

The dissertation is written very well and is readable with pleasure. The interpretation of the obtained results is convincing. I have no significant remarks, but only one suggestion for future research of the candidate on the subject. More and more literature data show that the degree of solubilization of drugs in the micelles depends to a large extent on the shape of the micelles. In this regard, I believe that in order to more in depth characterization of these systems, it would be interesting for the candidate to envisage future research to clarify this relationship.

Scientific-metric indicators related to the dissertation

The results described in the dissertation are reflected in two publications in renowned in the field of pharmaceutical technology journals with high impact factor and have been reported at 9 international scientific forums. The quality of the doctoral student's works is also evidenced by the 42 citations of the above mentioned articles noticed in the scientific literature. The doctoral student has participated in 10 research projects funded by national and European funds, as well as funds from the industry. The doctoral student is a scientific supervisor of two of the aforecited projects.

Dissertation summary

The dissertation summary reflects very accurately and clearly the results and contributions of the dissertation.

CONCLUSION:

The dissertation of Zahari Penkov Vinarov entitled "*Improving the solubility of hydrophobic drugs by solubilization in surfactant micelles*" contains original results with a contribution to optimizing oral drug delivery. The detailed analysis and the indisputable quality of the dissertation show that the doctoral student has in-depth theoretical knowledge and professional skills in the field of scientific specialty "Technology of drug dosage forms and biopharmacy". Zahari Vinarov shows erudition and professional skills for the independent formulation of scientific hypotheses, conducting research and correct generalization and interpretation of the results.

I believe that the candidate fully meets the quantitative criteria for awarding educational and scientific degree "Doctor", as defined in the relevant regulatory framework, namely the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the General regulation on its implementation and the Institutional regulations for the application of the aforementioned law at Sofia University “St. Kliment Ohridski”.

Based on the above, **I confidently give my positive assessment of the dissertation and recommend the esteemed members of the scientific jury to vote positively for awarding the educational and scientific degree "Doctor" to Zahari Penkov Vinarov in professional field 7.3 Pharmacy and the scientific specialty "Technology of dosage forms" and biopharmacy ”**

Sofia, February 13, 2021 Reviewer:

/Prof. Denitsa Momekova/