R E V I E W

From prof. Dimitar Rachev Rachev, Doctor of Pharmacy, retired lecturer from the academic staff of the Faculty of Pharmacy of Medical University – Sofia, appointed as a member of the scientific committee with decree No. РД-38-454/.21.09.2021 of the Rector of Sofia University.

On the topic of the recruitment procedure for the academic position of "associate professor" in higher education area 7. "Healthcare and sport", professional field 7.3 "Pharmacy" (Pharmaceutical technology and biopharmacy), attached to the Department of Chemical and Pharmaceutical Engineering, Faculty of Chemistry and Pharmacy of Sofia University "St. Kl. Ohridski", announced in issue 63/30.07.2021 of the Bulgarian state gazette.

Only one candidate has applied for the announced associate professor position – **senior assist. prof. Zahari Penkov Vinarov, Doctor of Pharmacy, Doctor of Chemistry**.

I. Analysis of the carrier path of the candidate

Zahari Penkov Vinarov graduated in 2009 with a Master's degree in Pharmacy from Medical University - Sofia. Since 2011 he has been working as a researcher in the Department of Chemical Engineering at the Faculty of Chemistry at Sofia University. In 2014 he defended his doctoral thesis in chemistry on "In vitro studies of triglyceride lipolysis in the gastrointestinal tract." Since 2014 he has been an assistant, and since 2016 - senior assistant in the Department of Engineering Chemistry and Pharmaceutical Engineering, Faculty of Chemistry and Pharmacy at Sofia University. Since 2019 he has been a postdoctoral fellow in Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium. At the beginning of 2021 Zahari Vinarov successfully defended his doctoral thesis in professional field 7.3. "Pharmacy" (Pharmaceutical technology) on "Improving the solubility of hydrophobic drugs by solubilization in surfactant micelles" and acquired the educational and scientific degree "Doctor of Pharmacy".

The candidate has published 20 articles in journals with impact factor. He has participated in 19 research projects, 17 of which are international. He is a member of the editorial boards of specialized, internationally recognized journals and prominent professional organizations.

II. Description of the presented documents

The candidate has submitted a complete and chronologically arranged set of documents and materials, in connection with the competition, in electronic version, according to Article 107 of the "Regulations on the terms and conditions for obtaining scientific degrees and holding academic positions at Sofia University "St. Kliment Ohridski".

III. Criteria for assessment of the research activity of the candidate

1. Acquired educational and scientific degree "Doctor" (indicator group A)

Zahari Vinarov has obtained the educational and scientific degree "Doctor of Pharmacy" (Diploma № СУ 2021-24/15.03.21). The topic of the dissertation "Improving the solubility of hydrophobic drugs by solubilization in surfactant micelles" fits the scientific specialization required of the competition.

2. Habilitation essay (indicator group C)

The habilitation essay presented by the candidate is a monograph on "Solubilization: fundamental principles and biopharmaceutical applications", ISBN 978-954-07-5307-2, University Publishing House "St. Kliment Ohridski", 2021, in press.

The individual point score of Zahari Vinarov according to this indicator is 100 points, which satisfies the requirements established by "Recommended criteria for associate professor in 7.3. Pharmacy" of Sofia University of 100 points.

3. Books, publications and reports in specialized scientific journals (indicators from group D).

For this group of factors, senior assistant Zahari Vinarov presents:

3.1. Published book based on a defended PhD dissertation on the topic: "Mechanisms of solubilization of hydrophobic drugs from surfactants", ISBN 978-954-07-5298-3, University Publishing House "St. Kliment Ohridski", 2021, in press. This indicator provides the candidate with 40 points.

3.2. Publications and reports published in scientific journals, referenced and indexed in internationally recognized scientific databases.

20 scientific publications indexed in SCOPUS and Web of Science databases with impact factor (JCR, Clarivate®) are presented. Five of the publications are related to the attainment of doctoral degrees.

The personal point asset of the candidate, based on the other 15 (fifteen) publications, is 163 points. The total impact factor (IF) of the submitted publications is 112.8, and his individual impact factor is 18.

The individual point asset of the candidate according to indicators from group "D" is 203 points with the minimum required by the "Recommended criteria for associate professor in 7.3. Pharmacy" of Sofia University - 200.

4. Citations (indicators from group E).

According to the full bibliographic reference provided by Scopus (full description of the cited and cited articles), via the Catholic University of Leuven (KU Leuven) Belgium, Zahari

Vinarov has 319 citations on 18 of his presented publications. Based on them, he scores 4785 points (minimum requirements 50).

5. Indicators from group F.

5.1. Scientific projects

Senior assistant Zahari Vinarov has participated in **19 (nineteen)** research projects, of which 17 (seventeen) are international. Fourteen of them are applied research projects with industry, funded by foreign companies.

6. Other scientific and applied science assets of the candidate

6.1. Participation in scientific forums

40 participations in scientific forums at home and abroad were presented, with oral reports and posters.

6.2. Membership in an authoritative creative and/or professional organization in the respective scientific field

Zahari Vinarov is a member of the following professional organizations:

• European Pharmacopoeia (EDQM), expert group 13H (Oils and derivatives, polymers), from 2019;

• Member of the core-group in the project COST CA16205 "European Network for Understanding gastrointestinal absorption-related processes" and co-leader of working group 3 - advanced formulations;

• European Federation of Pharmaceutical Sciences (EUFEPS), 2013 - 2018;

• American Association of Pharmaceutical Researchers (AAPS), since 2012.

6.3. Participation in editorial boards

• Member of the editorial board of the Journal of Pharmacy and Pharmacology (Wiley / Royal Pharmaceutical Society) since 2020.

• Member of the Molecules Editorial Board (MDPI), since 2020.

• Member of the editorial board of Frontiers in Drug Delivery (Frontiers) since 2021.

IV. Teaching activity

Zahari Vinarov has five years of teaching experience, of which two years as an assistant and three years as a senior assistant at the Department of Chemical and Pharmaceutical Engineering, Faculty of Chemistry and Pharmacy at Sofia University "St. Kl. Ohridski".

His total teaching load for the five years (2014-2019), according to an official report, is 2766 hours of classroom teaching. The predominant part of the classroom teaching (over 90%) was related to practical exercises in "Pharmaceutical Technology".

Senior Assistant Zahari Vinarov has been a research supervisor of 4 (four) diploma theses (2 of which of foreign students in the Erasmus program) and 1 bachelor's thesis. He is a member of the team for preparation of the doctoral program in "Pharmaceutical Technology and biopharmacy" at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kliment Ohridski"

V. Evaluation of the research activity and the contributions of the candidate

The analysis of the scientific output of Zahari Vinarov shows that his theoretical and practical contributions are mainly in the field of pharmaceutical technology and biopharmacy and in particular in the following areas:

1. Improving the aqueous solubility of hydrophobic drugs by solubilization in colloidal aggregates

The challenge to increase the solubility of poorly water-soluble drugs is central for the modern pharmaceutical science and industry. In this regard, solubilization is one of the methods to solve it.

In a number of his studies the candidate clarifies the effects of the chemical structure of surfactants and drugs on the solubilization capacity of the micelles for fenofibrate, itraconazole, albendazole, progesterone, danazol, ibuprofen. It was found that the solubilization capacity of the surfactant micelles increases with increasing the length of the hydrophobic tail of the surfactant for all studied drugs. The hydrophilic head of the surfactant also affects the solubilization, because of the interactions between the drug and surfactant molecules. The obtained results show a strong dependence of drug solubilization on the molecular structure of surfactants and provide an interpretation at the molecular level of the mechanisms and interactions that control these processes. The solubilization of drugs in solutions of natural surfactants (saponins) was also studied, and it was found that bidesmosidic triterpenoid saponins significantly improve the solubility of fenofibrate and danazol.

All these studies, with added new data and comparisons with the literature, are summarized and discussed in detail in the candidate's monograph "Solubilization: fundamental principles and biopharmaceutical applications". The monograph gives a comprehensive view of the solubilization of drugs in colloidal aggregates of surfactants in the context of pharmaceutical technology and biopharmacy. The monograph provides new data and dependencies that allow rational selection of surfactants for drug solubilization.

2. Oral lipid-based drug delivery systems

Lipid-based drug delivery systems (LBDDS) are one of the modern pharmaceutical technologies used to improve the solubility and bioavailability of poorly water-soluble drugs. Some of the main problems in the pharmaceutical development and in vitro studies on such

systems have been analytically considered by the candidate in the review “Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network”, published in Advanced Drug Delivery Reviews (2021).

In his research, in this direction, the candidate studies the influence of the lipid carrier and the size of the droplets on the drug release profile in an in vitro model of the gastrointestinal tract. It has been found that when using long-chain triglyceride oils, the drug release is determined by its solubilization in mixed colloidal aggregates of bile salts and triglyceride lipolysis products. The reduction of emulsion droplet size was found to accelerate the process. On the other hand, supersaturated drug solutions are obtained when the drug is formulated as an oil emulsion composed of medium chain triglycerides. In this case, the size of the droplets in the emulsion has a negative effect: smaller droplets lead to faster drug precipitation and a lower maximum in the concentration of released drug.

The role of phospholipids and triglyceride lipolysis products on drug solubilization has been investigated in detail in another publication of the candidate. The results for 13 phospholipids, 11 fatty acids and 2 monoglycerides show that unsaturated long chain lipids very strongly increase the solubility of hydrophobic drugs, while long chain saturated lipids have a negligible effect due to the different mechanism of drug solubilization, which depends on the formation of mixed micelles of lipids with the bile salts, which in turn is controlled by the melting point of the lipid. The conducted studies provide an opportunity for rational selection of lipids in order to achieve maximum drug solubilization in the gastrointestinal tract.

The candidate's contribution in this area is also related to the development of a fundamentally new approach for obtaining nanoemulsions by cyclic melting/hardening of a coarse emulsion. This method can be successfully used to prepare nanoemulsions in the field of lipid drug delivery systems.

3. Biopharmaceutical methods for assessment of oral formulations

The problems faced by modern biopharmaceutical research are related to the possibility of maximum approximation of the "in vitro" conditions of the experiment with those in a living organism, which would allow for predictable behavior of the active pharmaceutical ingredient, the excipients and the formulation after oral administration. The challenges in this direction are related to the many variables in the "in vivo" conditions of the gastrointestinal tract (GIT), which are both physicochemical, anatomical and physiological. Huge scientific potential in recent years has been concentrated in this area.

The candidate has his contribution in this direction. His first published scientific article, in 2012, was related to the development of a new "in vitro" model that resembles GIT, namely by the use of bicarbonate buffer to maintain the pH in the intestinal phase and its change from 6.2 to 7.5, duration of the experiment of 4.5 hours, the use of bile salts and gastric and pancreatic enzymes. The effects of calcium ions and saponin extracts on the bioavailability of cholesterol were studied using a new in vitro model. The same model was used to study the effects of surfactants and their interactions with bile salts in the small intestine on drug solubility. It has

been shown that nonionic surfactants do not form mixed micelles with bile salts and their solubilization capacity gradually decreases with increasing the proportion of bile salts in the mixture. In contrast, the solubilization capacity of ionic surfactant micelles decreases dramatically with the addition of a small amount of bile salts, which leads to drug precipitation. The effect is due to the formation of mixed micelles with low drug solubilization capacity due to the strong interactions between ionic surfactants and bile salts.

It should be noted here that during the two-year period from 01.10.2019 to 30.09.2021, the candidate worked on the project "Robotic methods for complete physiological characterization of the pharmaceutical action" with a leading organization Janssen Pharmaceutica. The results obtained by the candidate include the development of four methods for biopharmaceutical research of oral drugs, which are integrated into the processes of development of oral dosage forms in Janssen Pharmaceutica.

VI. Summarized assessment of the research and teaching activities of the candidate

The research activity of senior assistant professor Zahari Vinarov is mainly focused on the study of the possibilities for increasing the solubility of hydrophobic drugs through the methods of solubilization and lipid-based drug delivery systems. He has undeniable contributions in this area, both in scientific and in scientific-applied aspect. An additional asset of the candidate are his developments with scientific and practical application, namely the research on the development of biopharmaceutical models in bioequivalent environments.

The candidate is the first author in 11 of his publications, which confirms his ability to independently plan and conduct research. Most of the publications are in collaboration with foreign researchers, which shows that the candidate is recognizable in his scientific field and has the necessary teamwork skills.

Regarding his teaching activities, I can note that he is an established teacher in the university with more than 5 years of teaching activities related to the training in "Pharmaceutical technology and Biopharmacy" for Pharmacy students.

Based on the documents and materials submitted for review and the performed analysis, my summary assessment is that **senior assistant professor Zahari Penkov Vinarov** has the necessary **scientific and teaching experience** to hold the academic position of "Associate Professor". according to the requirements of Bulgarian law and of "Recommended criteria of Sofia University" St. Kl. Ohridski for professional field 7.3. Pharmacy", for which I also present a comparison table.

Group of indicators	*Requirements for the award of the academic appointment "associate professor", according to the recommended criteria of Sofia University" St. Kl. Ohridski for professional field 7.3. Pharmacy (05.11.2019)*	*For the candidate, senior assist. prof. Zahari P. Vinarov*
A	50 points	50
- C	100 points	100
D	200 points	203
E	50 points	4785
F	-	385
Teaching experience	2 years	5
IF	-	112.8 (personal 18)
First author (No. of articles)	-	11

VII. CONCLUSION

The analysis of the scientific and teaching experience of **Senior Assistant Professor Zahari Penkov Vinarov, Ph.D**. show that the candidate **FULLY MEETS** the requirements of Bulgarian law and of the "Recommended criteria of Sofia University St. Kl. Ohridski for professional field 7.3. Pharmacy" for holding the academic position of Associate Professor:

1. Has acquired PhD in Pharmacy in 2021.

2. He has five years of taching experience as an assistant and senior assistant professor at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kl. Ohridski "

3. There is a presented monograph

4. He meets the minimum national requirements and the additional requirements of Sofia University "St. Kl. Ohridski"

Based on all of the above, <u>I present a positive review</u> and I recommend to the members of the scientific jury to choose Senior Assistant Professor Zahari Penkov Vinarov, Ph.D., for the academic position of "Associate Professor" in the professional field 7.3. "Pharmacy", scientific specialty "Pharmaceutical technology and biopharmacy" to support the teaching at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kl. Ohridski".

22.11.2021

Sofia (Prof. Dimitar Rachev, Ph.D.)