MEDICAL UNIVERSITY OF SOFIA
FACULTY OF PHARMACY
1000 SOFIA, Dunav st. 2
www.pharmfac.net

O P I N I O N

by **Irini Atanas Doytchinova,** DSc.,

Professor in the Faculty of Pharmacy at the Medical University of Sofia

RE: PhD thesis of Zahari Penkov Vinarov, PhD student in the Faculty of Chemistry and Pharmacy, University of Sofia, on theme: Increasing the solubility of hydrophobic drugs by solubilisation in micelles of surfactants, submitted for awarding a PhD degree in the area of higher education: 7. Healthcare and sports, professional direction: 7.3. Pharmacy, doctoral program: Technology of drug formulations and Biopharmacy

The PhD thesis of Zahari Vinarov, MPharm, is the field of surface physicochemistry and is focused on developing of drug delivery systems based on micellar structures of surfactants. The objects of the study are well-studied and widely used in therapeutic practice drugs of class II of the Biopharmaceutical Classification System. This class includes drugs with high permeability and low water solubility. The bioavailability of these drugs depends on the degree of dissolution, and the rate of absorption is determined by the rate of dissolution. The thesis examines the mechanisms of solubilization of three class II drugs – progesterone, danazol and fenofibrate – included in the micelles of 20 surfactants and the factors that influence the processes.

The dissertation is written on 77 pages. It contains 4 chapters: introduction, materials and methods, results and discussion. In addition, conclusions and contributions are given. It is illustrated with 4 tables and 33 figures. The bibliography includes 110 titles.

The chapter "Introduction" describes the biopharmaceutical aspects of oral administration of drugs, solubility, mechanism of dissolution and methods for increasing the solubility and dissolution rate. The solubilization by surfactants is described in details. This part of the introduction includes well-known information and is more suitable for a textbook than for a PhD thesis. The literature review is extremely short – a page and a half – and includes 24 references. The chemical structures of the tested compounds and quantitative

information about their solubility in water or saline are missing. The goal is clearly defined and the tasks reflect the research needed to achieve the goal.

The chapter "Materials and methods" describes techniques as high-performance liquid and gas chromatography used to determine the equilibrium drug solubility in presence of surfactants and to calculate the molar solubilization capacity of surfactants. A spectrophotometric method used to determine drug solubilisation locus in the micelles and a laser light scattering method used to determine the critical micelle concentration (CMC) and micelle size are also described. It is noteworthy that the experiments in the thesis do not require expensive equipment and chemicals, are easy to perform and give very clear results, which well analyzed and interpreted lead to valuable information about the effects of various factors on drug solubilization.

The results and discussion are given in two chapters. One deals with the solubilization of progesterone and the other – with the solubilization of fenofibrate and danazol. The effects of surfactant type (anionic, cationic, nonionic) on drug solubility, the effects of surfactant structure on the solubilization capacity, the type of intermolecular interactions between surfactants and solubilized drugs have been systematically studied. For progesterone, it was found that ionic surfactants have the highest solubilization capacity due to ion-dipole and hydrophobic interactions between drug and surfactant. These interactions are possible only if the progesterone molecule is located in the palisade layer of the micelle, which is proven by the effect of surfactant hydrophilic head group on the solubilization capacity.

The results for danazol are similar to those of progesterone due to their close steroid structures. Ionic surfactants show a higher solubilization capacity than nonionic ones. The danazol molecule is also located in the palisade layer and the interactions are ion-dipole and hydrophobic. Unlike steroid molecules, the effects of ionic and nonionic surfactants on solubilization of fenofibrate are similar. The fenofibrate solubilisation locus depends on surfactant type: in non-ionic surfactant micelles the drug molecule is located in the hydrophobic nucleus, in ionic surfactant micelles – in the palisade layer.

The results are clearly and accurately analyzed and interpreted, the conclusions follow logically. I would like to recommend the application of molecular modeling in your future research for determining drug-surfactant interactions. Molecular models provide a better understanding and illustration of the interactions.

Since thesis conclusions and contributions sounded the same to me, I reformulated the contributions in three directions:

- theoretical – the mechanisms of solubilization of three polar but hydrophobic drugs and the factors influencing the processes have been established;

- methodological – a methodology for determining water solubility, solubilization capacity and drug solubilization locus in the micelle has been developed, which is universal and can be used as a routine protocol for selection of a solubilizing agent in the development of dosage forms for class II drugs;

- applied – the developed methodology has been applied on three drugs of class II and the obtained solubilizates have shown solubility, several orders higher than the solubility of unsolubilized molecules.

Zahari has published two papers related to the thesis. Both are published in journals with IF, respectively in Q2 (20 points) and Q3 (12 points), which cover the required 30 points for the PhD degree, according to the Regulations for application of the law for the development of the academic staff in the Republic of Bulgaria. 39 citations were also detected in Scopus (excluding self-citations of selected author). By the time of preparation of this opinion, the citations were already 42.

I have known Zahari personally since his student years in the Medical University of Sofia and I follow his development in Prof. Nikolai Denkov's Lab. Zahari is a worthy member of this long-standing Lab of Chemical Engineering created over the years at the Faculty of Chemistry by great scientists like Acad. Kralchevski and Prof. Denkov.

I give a positive assessment of Zahari Vinarov's thesis and as a member of the scientific jury I vote positively for awarding him a PhD degree in the area of higher education: 7. Healthcare and sports, professional direction: 7.3. Pharmacy, doctoral program: Technology of drug formulations and Biopharmacy.

12.02.2021 Reviewer: 

Sofia (Prof. Irini Doytchinova)