# REVIEW

By **Prof. Rahamin Daniel Shekerdjiski, PhD**

Regarding: Competition for the occupation of the academic degree PROFESSOR in scientific discipline "Technology of the dosage forms", field of the higher education 7. Healthcare and sport, professional direction 7.3. Pharmacy, for the needs of the specialty "Assistant pharmacist" in Medical College of the Trakia University- Stara Zagora published in the State Newspaper vol 99/13.12.2022

During the competition only one candidate Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D. participated.

## Eligibility of the candidate

The first meeting of the Scientific Jury, which was held on 20.02.2023, after the competition materials had been provided to all members of the Scientific Jury before this meeting, accepted with a full majority that the scientific production provided by the only candidate Assoc. Prof. Krum Stefanov Kafedjiiski, PhD, regarding participation in the competition corresponds to the minimum national and additional requirements of the Regulations on the terms and conditions for acquiring scientific degrees and holding academic positions at Trakia University- Stara Zagora and allowed him to be evaluated in the competition.

## I. Short data of the candidate

Krum Kafedjiiski was born on 06 Nov 1977 in Dupnitsa. He graduated the English Language High School "Academic L. Stoyanov", Blagoevgrad and gained specialty in Pharmacy in MU-Sofia in 2002 (№ 012079/ 30.01.2003). He possesses a recognized SDO specialty in "PHARMACOLOGY AND PHARMACOTHERAPY, Medical University-Varna, Diploma № 4802/ 07.07.2022. During the period 2003- 2006, he was a PhD student in the Department of Pharmaceutical Technology of the Institute of Pharmacy, Leopold Franzens University of Innsbruck, Austria. In 2006, he successfully earned his Ph.D on the topic: Development and evaluation of novel excipients for multifunctional drug delivery systems".

The obtained scientific degree in Austria „Doctor rerum naturalium" in the scientific discipline Technology of the dosage forms and biopharmaceutics has been acknowledged by VAC (VAC Certificate from 11/2007). As a full-time PhD student at the Leopold Franzens University, Innsbruck, Austria, he supervised graduate students and conducted practical exercises with students in Technology of dosage forms and Biopharmaceutics. In the period 2008-2011, he specialized as a Post-Doc at Novo Nordisk, Copenhagen, Denmark. From 2015 he qualified as an ASSOCIATE PROFESSOR in the Department of "Pharmaceutical Sciences and Social Pharmacy", Sector "Technology of dosage forms" at the Faculty of Pharmacy of MU Pleven. From 2022 he was appointed as an ASSOCIATE PROFESSOR in "Technology of the dosage forms" in Medical College of the Trakia University- Stara Zagora.

He uses 4 languages: English, German, Danish and Russian. He is a member of the German Pharmaceutical Society (APV) and the American Association Pharmaceutical Society (AAPS).

## II. Assessment of the scientific and research activity

The candidate presents 31 scientific publications and 14 out of them are in foreign journals and 12 in Bulgarian as well as one habilitation work and four patents. 13 of the scientific publications are in journals with impact factor. In 18 scientific publications the candidate is a first author. After the acquisition of the accademic position ASSOCIATE PROFESSOR, he has published 12 scientific publications and in 11 of them is a first author. The total impact factor of the candidate is 57.5. In addition, he has 680 citations in Scopus database as well as 553 citations in the Web of Knowledge database. He also has participated in seven scientific projects with international and bulgarian funding, mutual scientific projects with Bayer GmbH, Germany and the Austrian NANO initiative.

## III. ASSESSMENT OF THE CANDIDATE'S CONTRIBUTIONS TO THE SCIENTIFIC RESEARCH AND SCIENTIFIC ACTIVITY OF THE CANDIDATE

The candidate's scientific output can be divided and summarized in the following 3 main directions:

1. **Laying down the foundations of original Thiomer technology for drug delivery systems (Drug Delivery Systems).** The technology is mainly based on thiolated polymer excipients called thiomers. The thiolated polymers are new hydrophilic polymers obtained by the covalent bonding of sulfhydryl ligands. Due to the immobilization of thiol groups on already well-established polymers such as polyacrylates or chitosans, the following characteristics are greatly improved: mucoadhesive properties, increased permeation effect, ability to provide a controlled drug release, enzyme inhibitory properties, in situ gelling properties, efflux pump inhibition.

    a. **Creation of a new mucoadhesion theory**. Until now all theories for the bioadhesion phenomenon are based on non-covalent bonds. In comparison with the well-established mucoadhesive polymers, these innovative polymers have the ability to create covalent bonds with the cysteine rich sub-domains of the mucus glycoproteins thus forming disulfide bonds between the mucoadhesive polymer and the mucus layer. For example, the resulting time of adhesion of Ch-GSH is approximately 166 hrs, which is more than 55 times improvemenr of the adhesion time in comparion with unmodified chitosan.
    b. **Permeation enhancing effect of the thiomers**. The likely mechanism, which is responsible for the increased permeation in the presense of the conjugate Ch-GSH, is based on the inhibition of the enzyme protein tyrosine phosphatase (PTP) by the reduced form of GSH. Results demonstrate a significantly improved permeation enhancing effect (4.9 times) of the system Ch-GSH/GSH in comparison with the unmodified chitosan.

c. **Inhibition of efflux pumps**. Thiomers significantly increase the absorption of lipophilic substrates of P-gp and multidrug resistance protein (MRP) like saquinavir. P-gp inhibitory effect has been demonstrated for various thiomers *in vitro* as well as *in vivo*.
d. **Transmucosal systems for controlled release.** It has been shown that the new thiomers exhibit exactly such features as well as it can be guaranteed an intimate contact of the thiomer with the embedded drug with the gastrointestinal mucus will take place.
e. **Development of a mucoadhesive gastrointestinal patch system.** In this patch system, the permeation enhancing and mucoadhesive features of the conjugate Ch-GSH are combined together with a protective coating layer.
f. **Development and evaluation of thiolated microparticles produced via the milling technique (Air Jet Milling)**. This method is composed of three consecutive steps of co-precipitation, pre-milling and jet milling. Protein horseradish peroxidase has been used as a model drug.

In confirmation of the potential of the thiomer technology, at about 500 publications have been published by about 50 different research groups proving the superiority of thiomers over the corresponding unmodified polymers. Besides that the first commercial product containing thiomer (Lacrimera®; Croma - Pharma) is already on the European and Canadian market since 2018. This product uses a thiomer based on hyaluronic acid, which was first synthesized by the author in 2007.

2. <u>**Development of a dosage form of insulin for oral administration,**</u> which development started during the specialization in Novo Nordisk, Copenhagen, Denmark. The development of oral peptide delivery systems has been a constant challenge for scientists due to their several unfavorable physicochemical properties, including large molecular size, susceptibility to enzymatic degradation, and short plasma half-life. Different formulation strategies were used in order to overcome these problems:

   a. Screening of absorption enhancers and enzyme inhibitors.
   b. Oral Insulin Self-emulsifying drug delivery systems (SEDDS) or SMEDDS, formulated as tablets. The new technology employs emulsifying system, which is adsorbed on a solid carrier and then it is formulated as a tablet with enteric coating.
   c. Hydrophobic ion-pair complex (HIP) of insulin derivative with anionic surfactant - sodium dodecyl sulfate, sodium decyl sulfate. It is proofed with this method that the hydrophobic modified insulin increases its absorption efficacy thru the mucosal membrane.
   d. Hydrophobic ion-pair complex (HIP) of insulin derivative with medium chain fatty acids permeation enhancer - sodium decanoate (sodium caprate)/ sodium octanoate (sodium caprylate). A 99% complexation efficacy has been achieved.
   e. Insulin Complexes in self-nano-emulsifying drug delivery systems (SNEDDS)/ Nanoemulsions.

In the new formulations two techniques are combined for the bioavailability improvement of insulin derivatives- hydrophobic ion-pairing (HIP) and self-nanoemulsifying drug delivery (SNEDDS) or nanoemulsions. All compositions are evaluated *in vivo*. For example when Insulin A- Sodium caprate/caprylate complex is in the nanoemulsion composition, which is composed of Diglycerol caprylate, Tween 20, Water, Sodium caprate, SBTI 1S, the best result of 38% bioavailability has been achieved. Such a high value of insulin bioavailability has not been reported in the scientific and patents literature. The high result of 22 % bioavailability of this composition has been confirmed in additional *in vivo* studies on male Beagle dogs after oral administration of enteric coated soft capsules, which contain this nanoemulsion.

**3. <u>Scientific and applied technological research with original nature:</u>**

a. Development of pharmaceutical compositions containing L-alpha-glycerylphosphorylcholine with nootropic therapeutic activity in the form of oral hard gelatin capsules and powder for oral solution. The research is protected with two patents.
b. Development of a stable pharmaceutical composition of an oral solution containing Metamizole sodium monohydrate. Based on the investigations, a product registration dossier of the product was prepared under the trade name Omalgin, oral drops solution, Danson-BG OOD. Date of first authorization is 25.10.2019.
c. Development and in vitro research of a new Alginate Raft - forming oral suspension, which offers effective symptomatic treatment of the clinical manifestations of GERD - acid regurgitation, increased gastric acidity, indigestion after food intake. Based on the research, a registration file of the medicinal product was prepared under the trade name Gastroprotect Raft oral suspension, Adifarm EAD, and a market authorization was obtained - 02.11.2015.
d. Development of a composition and process for the production of a gastro-resistant tablet with the release of a low dose of 100 mg acetylsalicylic acid in the intestinal tract. The medicinal product was introduced to the market under the trade name Acessal Protect 100 mg gastro-resistant tablets, Chimax Pharma EOOD.
e. Development of a pharmaceutical composition of a powder for oral solution containing Acetylcysteine. A pharmaceutically acceptable stabilizer of acetylcysteine has been identified. A new method of masking an unpleasant taste has been developed using the excipient Kleptose Linecaps 17 (maltodextrin) - Roquette. The medicinal product is on the market under the trade name AceCys 200 mg powder for oral solution and AceCys acute 600 mg powder for oral solution, Chimax Pharma EOOD;
f. A stable product with fixed properties has been developed in the form of oral tablets containing inosine acedoben dimepranol 500 mg as an active substance and with immediate release of the active substance. Inosine acedoben dimepranol (inosine pranobex) is an immunomodulator indicated for the treatment of viral infections. Based on the research, a product registration file of the product was prepared, in which a production authorization was issued under the trade name Ino-Protect 500 mg tablets, manufacturer Adipharm EAD, holder of the authorization for use TEVA Pharma EAD, Bulgaria, 10.05.2022;
g. A pharmaceutical composition of a syrup containing a double dose of Inosine acedoben dimepranol has been developed. The effect of reducing the sugar syrup

content was investigated in accordance with the European Guideline for the development of medicinal products intended for use in pediatrics in the treatment of pediatric patients suffering from diabetes. The product is registered in Bulgaria under the name Ino-Protect 100 mg/ml syrup, manufacturer Adipharm EAD, holder of the authorization for use TEVA Pharma EAD, Bulgaria, 10.05.2022;

## IV. TEACHING ACTIVITY

Since 2022- a lecturer in Technology of the dosage forms and biopharmaceutics in the Medical College of the Trakia University, Stara Zagora

2015- 2022- a lecturer in Technology of the dosage forms and biopharmaceutics in the Faculty of Pharmacy of the Medical University- Pleven

2003- 2006- managing practical exercises with students in Technology of the dosage forms and biopharmaceutics, Leopold Franzens University of Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology. He supervised diploma students in the Leopold Franzens University of Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology.

## V. CONCLUSION

The contributions of Assoc. Prof. Krum Kafedjiiski, PhD, are of a markedly original and scientifically applied nature. Scientific-theoretical contributions are related to the latest trends in the development of the technology of dosage forms - development of multifunctional systems using "smart" polymers to solve technological and biopharmaceutical problems. Also of interest are the scientific and practical developments that have found application in practice, some of which are patent protected. The quantitative requirements for the required minimum scientometric indicators for occupying the academic position "PROFESSOR" have been met according to the requirements of the Law on the Development of the Academic Staff and the Regulations of Trakia University- Stara Zagora.
In conclusion and on the basis of the positive evaluation of the scientific research activity, the teaching activity, the high scientific significance of the scientific works, the prospective scientific and applied contributions contained in them fully complying with the requirements of the ZRAS, the Rules for its Application (PPZRAS), as well as the Regulations for the development of the academic staff at Trakia University- Stara Zagora, gives me a reason to give a positive assessment and to recommend to the members of the scientific jury to vote positively and award Assoc. Prof. Krum Kafedjiiski, PhD the academic position "PROFESSOR" in Technology of dosage forms and biopharmaceutics at Trakia University- Stara Zagora.

Date: 22.03.2023

Reviewer:

/ Prof. Rahamin Daniel Shekerdjiski, PhD /