

STATEMENT

By Assoc. Prof. Valentina Belcheva, PhD

/Medical College of the Trakia University Stara Zagora/

(Internal member of the Scientific Jury, confirmed with Order № 303/07.02.2023 of the Rector of Trakia University Stara Zagora)

REGARDING: Competition for the occupation of the academic degree PROFESSOR in the 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;

With Order № 303/07.02.2023 of the Rector of Trakia University Stara Zagora, Prof. Yarkov, PhD, I have been appointed as an internal member of the scientific jury. According to the Protocol from the first assembly of the scientific jury, I am entitled to prepare a statement with regards to the procedure for occupying the academic position “PROFESSOR” in the discipline Technology of dosage forms in the Medical College of the Trakia University Stara Zagora.

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

I. Short data for the candidate

Assoc. Prof. Krum Kafedjiiski was born on 06 Nov 1977 in Dupnitsa. He graduated the Blagoevgrad English Language High School “Academic L. Stoyanov” in 1996. He graduated the Pharmacy specialty in MU-Sofia during 2002. Since 2022 he also obtained SDO specialty in “PHARMACOLOGY AND PHARMACOTHERAPY, Medical University-Varna. 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 in 2007. During the period 2008- 2011, he specialized Post-Doc in Novo Nordisk, Copenhagen, Denmark. Since 2015 he has habilitated as ASSOC.PROF. in the Department „Pharmaceutical science and social pharmacy“, Sector „Technology of dosage forms” in the Faculty of Pharmacy of the Medical University- Pleven. Since 2022 he has been appointed as ASSOC.PROF. in the „Technology of dosage forms” of the Medical College of the Trakia University Stara Zagora.

II. Evaluation of the research activity

In the current competition Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D has presented 31 scientific publications, 14 of which in foreign journals and 12 in Bulgarian as well as in 18 of them he is a first author. He also has submitted one Habilitation Work (Oral delivery of therapeutic peptides. New formulation approaches, 2022; ISBN 978-619-92000-6-3) along with four patents.

After getting the academic title „ASSOC.PROF.“, the candidate published 12 scientific articles and in 11 of them he is a first author. The total impact factor is 57.5.

He has participated in mutual scientific projects with scientist staff from the University of Copenhagen, Denmark, Bayer GmbH, Germany and in the Austrian NANO initiative, Programme line 1: Research and technological development in mutual projects.

According to their thematic direction, the articles and scientific contributions are divided into three categories:

1) Scientific and theoretical contributions with original nature

The main scientific interest and contribution is in the creation of the new original Thiomers technology for 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 (efflux pump) inhibition.

- Original thiolated polymers were synthesized like chitosan-thioethylamidine (Ch-TEA), chitosan-glutathione (Ch-GSH), poly(acrylic acid)-glutathione (PAA-GSH), hyaluronic acid-cysteine ethyl ester (HA-Cys) and pectin-cysteine conjugate (Pec-Cys);
- A new mucoadhesion theory has been developed;
- The enhancing permeation effect of thiomers has been investigated;
- It has been demonstrated that the thiomers are in position to reversibly inhibit the efflux pumps;
- It has been shown that the new thiomers exhibit very promising features for transmucosal systems of controlled release;
- A new mucoadhesive gastrointestinal patch system has been developed;
- Thiolate microparticles were developed and obtained via a milling technique (Air Jet Milling) consisting of three successive stages of co-precipitation, pre-milling and jet milling.

2) Development of dosage form of insulin for oral administration

The development of oral peptide delivery systems is based on the use of the following strategies:

- Hydrophobic ion-pair complex (HIP) of insulin derivatives with anionic surfactant - sodium dodecyl sulfate, sodium decyl sulfate. It is proved with this method that the absorption efficacy of the hydrophobic modified insulin is increased thru the mucosal membrane;
- Hydrophobic ion-pair complex (HIP) of insulin derivatives with medium chain fatty acids permeation enhancers - sodium decanoate (sodium caprate)/ sodium octanoate (sodium caprylate). A 99% complexation efficacy has been achieved;

- Insulin Complexes in SNEDDS/ Nanoemulsions;
- Oral Insulin SEDDS or SMEDDS, which are included in a tablet form. This new technology employs an emulsifying system that is adsorbed onto a solid carrier and then formulated into an enteric coated tablet.

All compositions are evaluated *in vivo* on Sprague-Dawley rats. The compositions of Insulin A- SDS Complex in nanoemulsions, developed via Design of experiments (DoE), demonstrated higher bioavailability up to 22% in comparison with the compositions with SNEDDS.

Even much better bioavailability results of 30% are achieved for the composition Insulin A- caprate complex in SNEDDS composed of Diglycerol Caprylate, Tween 20 and Labrasol. 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) Scientific and applied contributions of an original nature

- 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;
- 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;
- 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;
- 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, Chimaks Pharma EOOD;
- 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;

- 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;
- Development of a pharmaceutical composition of a syrup containing a double dose of Inosine acedoben dimepranol. The main problems in the development of a double-dose syrup (100 mg/ml) based on Inosine acedoben dimepranol are defined - testing of the solubility of the active substance necessary for the preparation of a more concentrated form of a syrup and stability of Inosine acedoben dimepranol with respect to degradation products. As a result, the optimal conditions and composition of the syrup were determined, through which the target characteristics of the syrup are achieved - masking the bitter taste of the active substance, a stable solution with the adopted dose of 100 mg/ml and with good organoleptic properties for oral pediatric use. 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.

III. Citability

There are identified in total 680 citations in Scopus database as well as 553 citations in the Web of Knowledge database.

IV. Teaching activity

Since **2022** Lecturer in Technology of the dosage forms and biopharmaceutics in the Medical College of the Trakia University, Stara Zagora

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

2003- 2006 Management of 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 Technology of the dosage forms and biopharmaceutics in the Leopold Franzens University of Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology.

V. Participation in clinical trials

Participation in more than 60 trials with the following pharmaceutical companies: Pfizer; Schering-Plough; Novartis, Roche, GSK, Biogen, Merion, Centocor, Nuron, Merck-Serono, Chiesi, Catalent.

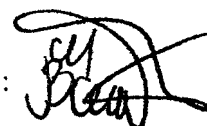
VI. Conclusion

Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D presented himself in the announced competition with a significant number of original publications, 1 habilitation work, 4 patents and numerous citations. The scientific work contain significant scientific-theoretical and applied contributions. The candidate has extensive teaching experience and academic workload. With all his data, Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D, fully covers and exceeds the uniform minimum requirements for holding the academic position "PROFESSOR", according to ZRASRB, the Regulations for the conditions and procedures for acquiring scientific degrees and holding academic positions at Trakia University Stara Zagora.

Everything stated so far gives me the reason to vote positively and fully convinced to propose to the esteemed Scientific Jury to elect **Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D** to the academic position of "PROFESSOR" in Technology of the dosage forms and biopharmaceutics fort he needs of the Medical College of the Trakia University, Stara Zagora.

Date: 20.03.2023

Member of the Scientific Jury:



/Assoc. Prof. Valentina Belcheva, PhD/