REVIEW

By Prof. Dr. Plamen Hristov Nenkov, Ph.D, Sofia, 38 Cherni Vrah Blvd

REGARDING: Competition for the occupation of the academic degree PROFESSOR in Technology of the dosage forms in Medical College of the Trakia University Stara Zagora in the field of the higher education 7. Healthcare and sport, professional direction 7.3. Pharmacy, for the needs of the specialty "Assistant pharmacist", 0.5 FTE published in the State Gazette vol 99/13.12.2022

During the competition for Professor in the Medical College of the Trakia University Stara Zagora, only one candidate Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D. submitted application.

BIOGRAPHICAL DATA

Krum Kafedjiiski was born on 06 Nov 1977. He graduated the Blagoevgrad English Language High School in 1996 and then obtained his master degree in Pharmacy from the Faculty of Pharmacy of the MU-Sofia in 2003 with honors and received the Master of Pharmacy qualification. In 2006, he earned his Ph.D. *(Doctor rerum naturalium - Dr. rer. nat.),* edition 48, № 796 from the *Leopold Franzens University of Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology* and in 2007 he received a Certificate from VAC regarding the recognition of the Scientific Degree "*Doctor rerum naturalium*", which was awarded in Austria for the scientific specialty 03.02.02- Technology of dosage forms and biopharmaceutics.

Specializations-

2000: Practical training in the composition formulation field, CETMED, Porto, Portugal

2008- 2011: Postdoc in Novo Nordisk, Copenhagen, Denmark.

He also has a recognized specialty in PHARMACOLOGY AND PHARMACOTHERAPY, Medical University-Varna, Diploma № 4802/07.07.2022

In 2015 he has been elected as **ASSOC. PROF.** in the scientific specialty Technology of the dosage forms and biopharmaceutics in the Faculty of Pharmacy of the Medical University- Pleven, Diploma № С 0039/06.07.2015.

Foreign languages

English- fluent verbal and written, German- very good verbal and written, Danish- good verbal and written, Russian- verbal and written

PROFESSIONAL ACTIVITY

2004- 2006 Internship in the specialty Master of Pharmacy in Sevex Pharma, Bulgaria

2006- 2008 Senior Clinical Research Associate, Quintiles, Bulgaria

2008- 2011 PostDoc specialization in Novo Nordisk, Copenhagen, Denmark

2011- 2012 Senior Clinical Research Associate, Worldwide Clinical Trials, Bulgaria

2012- 2015 Clinical Operations Manager, CTG Bulgaria EOOD

2015- 2017 Clinical Trial Manager, Novella

2017- 2022: Clinical Team Manager, PRA Bulgaria

Since September 2022 till now **ASSOC. PROF.** in the Medical College of the Trakia University **Stara Zagora**

SCIENTIFIC ACTIVITY:

The candidate presents 26 scientific publications and 14 out of them in foreign journals and 12 in Bulgarian. 13 of the scientific journals are with impact factor. In 18 scientific publications Kafedjiiski is a first author. After the acquisition of the accademic position Assoc. Prof, he has published 12 scientific publications in 11 of which he is a first author. He also presents one Habilitation Work and 2 review articles in foreign journals. Author of four patents.

The total impact factor of the candidate is 57.5. He has 680 citations in Scopus database as well as 553 citations in the Web of Knowledge database.

He also has participated in the development of seven scientific projects with international and bulgarian financing. He also took part in mutual scientific projects with scientists from the University of Copenhagen, Denmark and University of Antwerp, Belgium, mutual scientific projects with Bayer GmbH, Germany and the Austrian NANO initiative, programme line 1: Research and technological development in mutual projects.

A PhD thesis has been developed with the following title „Development and evaluation of novel excipients for multifunctional drug delivery systems"- 2003- 2006.

Scientific and theoretical contributions with original nature

The main scientific interest is the development of the new original Thiomer technology for drug delivery systems (Drug Delivery Systems) in a team with the leader Prof. Dr. A. Bernkop-Schnürch, Austria.

1. 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).
2. A new mucoadhesion theory has been created. 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. It is considered that the thiomers react with the cysteine rich sub-domains of the

mucus glycoproteins thus forming disulfide bonds between the mucoadhesive polymer and the mucus layer. 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.

3. It has been investigated the 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 effect (4.9 times) of the system Ch-GSH/GSH in comparison with the unmodified chitosan.
4. It has been demonstrated that thiomers are in position to reversibly inhibit the efflux pumps. The 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.
5. It also has been shown the new thiomers exhibit very promising features for transmucosal systems of controlled release. It can be guaranteed that an intimate contact of the drug with the mucus of the gastrointestinal tract will take place when thiomers are utilized.
6. A new mucoadhesive gastrointestinal patch system has been developed. In this system, the permeation enhancing and mucoadhesive features of the conjugate Ch-GSH are combined together with a protective coating layer.
7. Thiolated microparticles are developed and evaluated, which are produced via milling technique (Air Jet Milling), which is composed of three consecutive steps of co-precipitation, pre-milling and jet milling. Protein horseradish peroxidase has been used as a model drug.

The second direction is the development of dosage form of insulin for oral administration. This project is strategic for Novo Nordisk and research has been performed within the 3-year specialization- postdoctoral research in the company. The development of oral drug delivery systems for peptides is a constant challenge for pharmaceutical scientists due to their unfavourable physico-chemical properties including big size of the molecule, susceptibility towards enzymatic degradation, short plasma half-time. The absolute oral bioavailability of most of the peptides and proteins is less than 1%. To overcome these challenges different formulation strategies have been employed:

1. Screening of absorption enhancers and enzyme inhibitors.
2. 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.
3. 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.
4. Hydrophobic ion-pair complex (HIP) of insulin derivative with medium chain fatty acids permeation enhancer - sodium decanoate (sodium caprate)/ sodium octanoate (sodium

caprylate). The developed complexes are original. A 99% complexation efficacy has been achieved.

5. 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*- via injection into mid-jejunum of anaesthetized overnight fasted Sprague-Dawley rats.
Data indicate the achieved bioavailability (F) of the composition Insulin A- SDS Complex in SNEDDS (DC, Tween 20, DA) was 13%. However, the compositions of Insulin A- SDS Complex in nanoemulsion, developed via Design of experiments (DoE), demonstrated higher bioavailability up to 22% in comparison with the compositions with SNEDDS. The better results with nanoemulsions can be explained with the utilization of additional approaches for the composition compared with SNEDDS: use of permeation enhancer- 3% sodium caprate along with 2% SBTI 1S in aqueous solution. The protease inhibitor protects insulin from cleavage and enhances the absorption of Insulin in the guts. 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.
However 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.

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.

SPECIALIZATIONS, POSTDIPLOMA EDUCATION, GRANTS AND PRIZES

2003- 2006 Österreichische NANO Initiative, Programmlinie 1: Forschung und Technologieentwicklunj in Verbundprojekten

2009 SMEDDS development course, Copenhagen, Denmark

2010 Effective Project Management Course, Novo Nordisk
2011 Patent Short Course, Novo Nordisk
2010 Effective Presentation Skills for Medical Professional Programme, Paris
2011 Quality by Design Course, Novo Nordisk
2011 Factorial design: principle and applications, Novo Nordisk

CERTIFICATES: ICH- GCP, GMP, Inform, ClinDoc, CTMS, Inntrax, InFormant, European Clinical Trial directive 2001, FDA 21 CFR12

SCIENTIFIC INTERESTS: Thiomer technology, Development of non-invasive drug delivery systems of peptides and proteins; micro and nanoemulsions; lipid systems for drugs BSC II grade

PARTICIPATION IN SYMPOSIA: Over 30 participations in international conferences and symposia

PARTICIPATION IN CLINICAL TRIALS- above 60 with the following pharmaceutical companies: Pfizer; Schering-Plough; Novartis, Roche, GSK, Biogen, Merion, Centocor, Nuron, Merck-Serono, Chiesi, Catalent.

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS AND PARTICIPATION IN SPECIAL FORUMS:

2022 American Association of Pharmaceutical Scientists (AAPS)

2021 German Pharmaceutical Association APV

2022 Bulgarian Association of Clinical Trials BACT

2012- 2021 Participation in multiple Investigators meetings in the field of clinical trials

2012- 2021 Participation in meetings as a Manager of clinical trials

2009, 2010, 2011- 2022 Participation in AAPS meetings

2003- 2006 Participation in Controlled Release Society meetings

2005, 2009 Participation in Pharmaceutical Sciences Fair § Exhibition, Nice, France

CONCLUSION

In conclusion I consider that Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D is a highly qualified scientist and lecturer. The scientific research and lecturing activity of Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D fully responds to the announced direction of the competition, also to the requirements of the Law for the development of accademic staff in Republic of Bulgaria and the regulations for its implementation. In result of the abovementioned, I give my positive assessment and propose to the esteemed jury of the

competition to elect Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D for the accademic position „PROFESSOR“ in Technology of the dosage forms in Medical College of the Trakia University Stara Zagora in the field of the higher education 7. Healthcare and sport, professional direction 7.3. Pharmacy, for the needs of the specialty "Assistant pharmacist" and for which I will vote.

Date: 10.03.2023

Reviewer:

/ Prof. Dr. Plamen Hristov Nenkov, Ph.D/