REVIEW

By Assoc. Prof. Kaloyan Georgiev, PhD

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Member of the Scientific Jury based on Order № 303/07.02.2023 of the Rector of Trakia University- Stara Zagora. According to the Protocol from the first meeting of the scientific jury conducted on 20.02.2023, I have been entitled to prepare a review.

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

One candidate participated in the announced competition - Assoc. Prof. KRUM STEFANOV KAFEDJIISKI, PhD. The set of documents has been prepared in accordance with the requirements of the Academic Staff Development Act of Republic of Bulgaria (ASDARB), as well as the Regulations for implementation of the ASDARB (RIASDARB) and the Regulation for the conditions and order of acquiring of academic positions at Trakia University- Stara Zagora.

Brief biographical data

Krum Stefanov Kafedjiiski was born on 06 Nov 1977 in Dupnitsa. He graduated the English Language High School "Academic L. Stoyanov", Blagoevgrad. He graduated in Pharmacy specialty from MU-Sofia in 2002. He also possesses a recognized SDO specialty in "PHARMACOLOGY AND PHARMACOTHERAPY in 2022 from the Medical University-Varna. During the period 2003- 2006, he was a PhD student in 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", in result of that he was awarded in Austria the scientific degree „Doctor rerum naturalium" in the scientific discipline Technology of the dosage forms. 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 possesses good computer literacy. He also uses 4 languages: English, German, Danish and Russian. He is a member of the Bulgarian Association of Clinical Trials (BACT), German Pharmaceutical Society (APV) as well as the American Association Pharmaceutical Society (AAPS).

Educational and lecturing activity

Assoc. Prof. Krum Kafedjiiski has accumulated more than 20 years of experience in the specialty and more than 7 years of lecturing experience as a habilitated lecturer.

- 2003- 2006: Managing practical exercises with students in Technology of the dosage forms and biopharmaceutics, Leopold Franzens University, Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology. He supervised diploma students in the Technology of the dosage forms and biopharmaceutics, Leopold Franzens University, Innsbruck, Institute of Pharmacy, Department of Pharmaceutical Technology.
- 2015- 2022- a lecturer in Technology of the dosage forms and biopharmaceutics in the Faculty of Pharmacy of the Medical University- Pleven
- Since 2022- a lecturer in Technology of the dosage forms and biopharmaceutics in the Medical College of the Trakia University- Stara Zagora

Research and publication activity

For the present competition Assoc. Prof. Krum Stefanov Kafedjiiski, PhD presents 31 scientific publications and 14 out of them are in foreign journals, 12 in Bulgarian, in 18 of them he is a first author as well as one habilitation work and four patents. 13 of the scientific publications are in journals with impact factor. After the acquisition of the accademic position ASSOCIATE PROFESSOR, the candidate has published 12 scientific publications and in 11 of them is a first author. He also has developed a habilitation work on the topic: „*Oral delivery of Therapeutic peptides. New formulation approaches*", with year of publication: 2022.

In G and D indicators in the reference for the minimum national requirements concerning publication activity and citations, the points are significantly exceeded - 463 and 7730, with minimum requirements - 200 and 100, respectively, for both indicators. The candidate's overall impact factor is 57.5. To date, 688 citations have been established in the *SCOPUS* database (h index 11), as well as 558 citations in

the *Web of Knowledge* database (h index 10), which indicates the globally recognized importance of the author's published scientific production.

He has over 30 participations in international conferences and symposia as well as above 60 participations in clinical trials with the following pharmaceutical companies: *Pfizer; Schering-Plough; Novartis, Roche, GSK, Biogen, Merion, Centocor, Nuron, Merck-Serono, Chiesi, Catalent.* He also has participated in seven scientific projects with international and bulgarian funding. Also he took part in scinetiifc projects with Bayer GmbH, Germany and the Austrian NANO initiative.

According to their thematic direction, the scientific contributions can be divided and summarized in the following three categories:

1)<u>Thiomer technology for drug delivery systems (*Drug Delivery Systems*).</u>

This original technology is based on thiolated polymer excipients called thiomers. The thiomers represent new hydrophilic polymers obtained by the covalent bonding of sulfhydryl ligands. Due to the immobilization of these thiol groups on already well-established polymers such as polyacrylates or chitosans, their following characteristics are greatly improved: mucoadhesive properties, increased permeation effect, ability to provide a controlled drug release of the embedded drugs. Also increased are their enzyme inhibitory, in situ gelling properties as well as their effect on the efflux pump inhibition.

- **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 in practice, these innovative polymers have the ability to create covalent bonds with the cysteine rich sub-domains of the mucus glycoproteins and as a result of this interaction disulfide bonds between the mucoadhesive polymer and the mucus layer are formed.
- **Inhibition of efflux pumps**. It is indicated that 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*.
- **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.
- **Transmucosal systems for controlled release.** It has been shown that the new thiomers exhibit exactly such features as well as it can be guaranteed that an intimate contact of the thiomer with the embedded drug with the gastrointestinal mucus will take place.

- **Development 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.
- **Development of a mucoadhesive gastrointestinal patch system.** In this system, the permeation enhancing and mucoadhesive features of the conjugate Ch-GSH are combined together along with a protective coating layer.

2) Development of a dosage form of insulin for oral administration

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 employed in order to overcome these problems:

- Screening of absorption enhancers and enzyme inhibitors.
- Hydrophobic ion-pair complex (HIP) of insulin derivatives with anionic surfactants - *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.
- 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.
- Insulin Complexes in *SNEDDS*/ Nanoemulsions.
- *Oral Insulin SEDDS* or *SMEDDS*, which were formulated as tablets. The new technology uses emulsifying system, which is adsorbed on a solid carrier and then it is formulated as a tablet with enteric coating.

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. 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 technological research with 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. The research is protected with two patents.
- 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, Chimax Pharma EOOD.
- 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.
- 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

Conclusion

The scientific production of Assoc. Prof. Krum Stefanov Kafedjiiski, Ph.D, fully meets the requirements of the Academic Staff Development Act of Republic of Bulgaria (ASDARB), as well as RIASDARB and the qualitative and quantitative criteria for the development of the academic staff laid down in the Regulations of Trakia University- Stara Zagora for acquiring the academic position "PROFESSOR". The minimum requirements are fully covered for holding the position of "PROFESSOR", and in many of its scientific-metric indicators they exceed the quantitative criteria laid down in the Regulations of Trakia University- Stara Zagora. All this gives me the reason to give a **POSITIVE ASSESSMENT** and to propose to the respected members of the Scientific Jury to vote for awarding the academic position "PROFESSOR" in the field of the higher education 7. Healthcare and sport, professional direction 7.3. Pharmacy, regarding the needs of the Medical College of Trakia University- Stara Zagora, to Assoc. Prof. Krum Stefanov Kafedjiiski.

Town of Varna

20.03.2023 .....

/Assoc. Prof. Kaloyan Dobrinov Georgiev, Ph.D/