МЕДИЦИНСКИ УНИВЕРСИТЕТ
ПЛОВДИВ
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STATEMENT OF OPINION

by prof. Nikolay Georgiev Lambov, PhD – Faculty of Pharmacy, Medical University – Sofia

of a dissertation work for awarding the educational and scientific degree "Doctor"

Professional area: 7.3. Pharmacy

Doctoral program: Pharmaceutical Technology and Biopharmacy

Author: Yana Zhekova Gvozdeva

Form of the doctoral program: independent study form

Department: Pharmaceutical Sciences, Faculty of Pharmacy, Medical University - Plovdiv

Thesis: "Approaches for Taste Masking of Enalapril Maleate in Orodispersible Tablets for Pediatric Practice"

Scientific supervisor: prof. Margarita Kassarova-Traykova, PhD, Faculty of Pharmacy, Medical University – Plovdiv.

1. General introduction of the procedure and the doctoral student

The presented materials /on paper and electronic carrier/ completely correspond to the Regulations for Academic Development in MU-Plovdiv, 2021 /Article 70 (1), Section I – Obtaining the Educational and Scientific Degree "Doctor"/. The documents have been precisely prepared and include the whole necessary information.

The doctoral student has enclosed 4 published research papers.

Professor assistant Yana Gvozdeva graduated from the Faculty of Pharmacy, MU-Plovdiv. in 2015 as a Master of Pharmacy. The same year she was appointed a professor assistant in the Department of Pharmaceutical Sciences of the Faculty of Pharmacy, MU-Plovdiv. In 2020 she obtained the specialty "Pharmaceutical Technology with Biopharmacy".

Professor assistant Gvozdeva was enrolled as a doctoral student in an individual form of preparation in the doctoral program "Pharmaceutical Technology and Bio-pharmacy" in 2019 (Order № P- 388/11.03.2019 of the Rector of MU-Plovdiv). In 2021 she was checked off with a right of thesis defense (Order P-555/20.04.2021). As a doctoral student she has participated in the educational project "Doctor-2" at MU-Plovdiv.

Professor assistant Gvozdeva has participated in the development of one national research project and two inter-university research projects.

She has provided training moblities numerous times under the Erasmus program in leading European universities (Wien, Bratislava, Istanbul) and has taken part in specialized seminars (Fot expo, Eudragit), which has undoubtedly contributed to her excellent professional preparation in the field of pharmaceutical technology.

She has a high level of language proficiency in English and German.

2. Relevance of the subject

The thesis topic is definitely a question of present interest and significant for the pharmaceutical and clinical practice. The creation of specific pharmaceuticals for children is extremely important for achieving high effectivity and safety of the therapy. With relation to this, the development of fast orodispersible tablets (ODT) is of a special interest, because they combine the advantages of the solid dosage forms with the possibility of unproblematic intake for the children. Except for the obtainment of rapid disintegration (less than 3 min.), another serious technological problem is the correction of the unpleasant taste of the drugs, especially those with a bitter taste.

The presented dissertation work aims at solving those problems for a particular medicinal substance – enalapril maleate.

3. Knowledge of the problem

The literature review and analysis show that the student has thorough knowledge of the peculiarities and problems related to the development of fast-disintegrating tablets for oral application and the bitter taste masking of drugs, as well as technological approaches for their solving. This is obvious from the chosen research methodology and the conducted studies, the conclusion and analysis of the received results.

4. Research methodology

Undoubtedly, the chosen research methodology allows the aim achievement and the related task solving. An interesting and appropriate approach is the creation of microparticles, which could mask the bitter taste of the active substance. Methods for their preparation, as well as the description of their chemical, physico-chemical and bio-pharmaceutical characteristics were well selected, precisely described, in order to guarantee high level performance of the aim and tasks. There was used an appropriate approach for the creation of "super" disintegrants from dry plant extracts.

5. Characteristics and evaluation of the dissertation work and its contributions

The dissertation work, presented for my personal opinion, was written in 140 pages and illustrated with 49 figures and 35 tables. Especially, I would like to notice that it was structured very well.

The thesis structure completely corresponds to the Procedure for acquiring the educational and scientific degree of Doctor in MU-Plovdiv, 2021, and includes the required basic parts: introduction, literature review, aim and tasks, materials and methods, results and discussion, conclusions, contributions, used references and applications.

The Introduction is short but it introduces with competence the subject-matter of the dissertation work describing the specificity of preparing pediatric dosage forms for peroral application and the related problems.

The Literature Review is written with competence. The rich literature materials (165 literature sources) range over the last ten years. It is obvious that the PhD student has excellent knowledge on the subject-matter and is capable of making analyses and conclusions.

Materials and Methods. They are up-to-date, precisely and punctually described, and they guarantee the completion of the aim and tasks.

It refers to the preparation of microparticles with enalapril maleate, which are well selected in order to guarantee the receiving of reproducible results and their description. There were used the most modern chemical and physico-chemical methods – scanned electronic microscopy (SEM), powder x-ray diffraction (XRD), infrared spectroscopy (FTIR), thermal analysis (TG-DTA) and *in-vivo* methods for taste evaluation.

Results and Discussions. The conducted studies can be grouped into the following three directions:

1. There were conducted studies for preparing and characterizing polymer microparticles with enalapril maleate, which mask the bitter taste of the drug with the use of three basic preparation methods – precipitation, emulsion technique followed by solvent evaporation, and spray drying. There were examined several models with different enalapril maleate to polymer (Eudragit EPO®) ratio. The complexes obtained by the precipitation method have no satisfactory effect despite of the quantitative proportions. With regard to the emulsion technics, after the addition of second structural polymer (ethylcellulose) there were obtained microparticles with proper form and appropriate size. They mask the taste satisfactory, but at the expense of very low encapsulation efficiency. The best results have been observed in the modifying method of spray drying, which allows the elimination of the organic solvent. The obtained polymer microparticles with Eudragit EPO® (ratio of drug to polymer 1:6) were characterized with optimum properties as follows: technological (mean size 9.10 μm, loading 13.39 %, encapsulation efficiency 95.41 %), biopharmaceutical (quantity of free enalapril in saliva 1.81 % and in gastric juice 78.33 % per 150 min.), organoleptic.

2. There were obtained dry plant extracts from flax and quince seeds. The maceration temperature effect was examined, as well as the parameters of the drying regime on yields (flax seeds – 67% and quince seeds – 79 %). The content of polysaccharides in extracts provides high swelling index (this is a prerequisite for the successful use of super disintegrants in tablet preparation).

3. There were created tablet solid dosage forms for oral application by the method of direct tableting. The tablets were prepared using different quantity of the included dry extracts of flax and quince seeds (0.5% - 2 %). It was established that the lowest concentration provides the fastest disintegration (50 – 60 s). As a result of the implemented studies, as an optimum model was defined the one containing 0.5 % polysaccharides form flax seeds, which disintegrate very fast (50 sec.), wetted very fast (20 sec.) and had high water absorption ratio (23.1 %), releasing 92 % enalapril maleat within 45 min. The volunteers estimated it with the best bitter taste masking.

Conclusions. The conclusions that were presented are correct and they completely and accurately reflect the received results.

Contributions and significance of the dissertation work to science and practice: The scientific and scientific-applicable contributions of the dissertation can be listed as follows:

1. There were established the opportunities for bitter taste covering of enalapril maleate with the inclusion of polymer micro-particles with Eudragit EPO® received by a modified method of spray drying after eliminating organic vehicles (dissolvents);

2. There were recorded optimal parameters for receiving dry plant extracts form flax and quince seeds by the method of spray drying. It was proved that they can be applied as superdisintegrants in orodispersible tablets;

3. There was proposed an optimum model of fast orodispersible tablets (50 sec.) for the pediatrics practice based on taste corrected polymer microparticles with enalapril maleate and dry extract from flax seeds used as a disintegrant, having very good technological, biopharmaceutical and organoleptic properties;

4. From the summary of the received results, it can be concluded that the created solid dosage form with enapril maleate can be used in pediatric practice. The applied approach for its development can be used in the preparation of fast disintegrating solid dosage forms for oral application with other problematic drugs.

The part with references has been formed accurately and in correspondence with the requirements.

6. Evaluation of the scientific publications and the individual contribution of the doctoral student

The implemented studies and received results have been included in **4** publications, **2** of them in international scientific journals – **1** in referenced journal (*Folia Medica*) and **1** in impact factor journal (*Die Pharmazie – Int.J.Pharm.Sci.* IF=1.198). The research papers reflect a considerable part of the experimental studies in the dissertation.

The total number of points received from publications is 37.5 out of minimum 30 points required in ADASRB for the scientific degree "Doctor".

Two of the publications have been cited three times 3. Two of the citations are in Scopus journals.

The applicant has presented her studies on 12 scientific forums – 4 international (Hungary, Greece and Germany) and 8 in Bulgaria. Two of them were in English language.

Professor assistant Gvozdeva has participated in 1 inter-university project under the topic of the dissertation work.

In my opinion, the doctoral student has personal contribution to the research studies related to the preparation of orodispersible tablets with enapril maleate, with their detailed technological and biopharmaceutical description. Taking into account the complexity of studies, some of them were implemented in collaboration with specialists from other departments, who were mentioned in the dissertation work. Nevertheless, I think that she has a leading role in their organization and result discussion.

I have no critical notes. In the discussion process I have made some notes related to the technical construction and some notes related to the summary of the dissertation work. They were taken into account in the final dissertation version. As a whole, my positive assessment of the dissertation work remains unchanged.

7. Summary of a dissertation

The summary has been formed in accordance with the requirements of MU-Plovdiv Regulations. It adequately reflects the dissertation contents. It consists of the main results received from the conducted studies, the summaries and the conclusions. The scientific contributions correspond to those presented in the dissertation work.

CONCLUSION

The dissertation work contains *scientific, scientific-applicable and applicable results, which are original contributions in science* and **correspond to all requirements of** the Act for Development of the Academic Staff in the Republic of Bulgaria (ADASRB), the Regulations for Application of ADASRB, and the Regulations of the Medical University – Plovdiv. The presented materials and dissertation results conform **completely** with the specific requirements of the Regulations for Application of ADASRB in MU-Plovdiv.

The dissertation shows that the doctoral student Yana Gvozdeva possesses in-depth theoretical knowledge and professional skills necessary for the doctoral program "Pharmaceutical Technology and Biopharmacy". She demonstrates qualities and skills to implement individually scientific research.

With the above-mentioned, I state my ground to give a positive assessment to the dissertation, the summary, the obtained results and contributions. I am completely convinced to propose to the honorable scientific panel to award Yana Zhekova Gvozdeva the educational and scientific degree "Doctor" in the doctoral program "Pharmaceutical Technology and Biopharmacy".

19.05.2021

Reviewer: .....

/prof. Nikolay Lambov, PhD/