МЕДИЦИНСКИ УНИВЕРСИТЕТ
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REVIEW

by

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Medical University – Sofia, Faculty of Pharmacy
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Of a dissertation work for awarding the educational and scientific degree "**Doctor**"

Field of higher education: 7. Healthcare and Sport
Professional area: 7.3. Pharmacy

Doctoral program: Pharmaceutical Technology and Biopharmacy

Author of the dissertation work: Yana Zhekova Gvozdeva

Form of the doctoral program: independent study form

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

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

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

General introduction of the procedure and the doctoral student

A set of materials was presented on electronic carrier, which is in conformity with the Regulations for Academic Development at the Medical University – Plovdiv (Section I, Art. 70 (1), 2021) and includes all necessary documents.

The doctoral student enclosed 4 (four) publications.

Short biographical data of the doctoral student

Yana Zhekova Gvozdeva graduated from the Faculty of Pharmacy at MU-Plovdiv in 2015 with the educational and qualification degree *Master of Pharmacy*. In 2020 she obtained the specialty Pharmaceutical Technology with Biopharmacy. In 2018 Yana Gvozdeva participated in a seminar organized by Evonic Company related to the work with Eudragit polymers. The doctoral student realized several short specializations at European universities under the Erasmus program:

- Wien University (2016)
- Komen University of Bratislava (2017)
- Bezmialem Vakif University of Istanbul (2019)

Yana Gvozdeva participated in 5 scientific projects: University Center *Projects* at MU-Plovdiv, Young Scientists of University Center *Projects* at MU-Plovdiv, national scientific project Personalized Innovative Medicine (PERIMED), national educational project with European financing (Doctoral Student Training at MU-Plovdiv for Competence, Originality, Realization and Academism in Science and Technologies – 2 (DOCTORAL STUDENT - 2)) and the project Student Practices – Phase 2, financed by Operative Program Science and Education for Intelligent Growth.

In 2019 with Rector's order № P-388/11.03.2019 she was enrolled as a doctoral student in individual form of preparation in field of higher education 7. Healthcare and Sport, professional area 7.3. Pharmacy, doctoral program Pharmaceutical Technology and Biopharmacy at the Department of Pharmaceutical sciences, Faculty of Pharmacy, MU-Plovdiv, with scientific supervisor prof. Margarita Kassarova-Traykova, PhD. The doctoral student was checked off with the right of thesis defense with Rector's order № P-555/20.04.2021.

Subject matter relevance and expedience of the set aims and tasks

The dissertation work is dedicated to the development of taste corrected and effective orodispersible tablets for pediatric practice, which contain enalapril maleate. On the one hand, the research aims at evaluating different techniques for bitter taste masking of the drug, and on the other hand an achievement of fast tablet disintegration with the use of disintegrants of natural origin. The subject matter is extremely relevant and up-to-date because of the fact that at present, in pediatric practice there is lack of an appropriate pharmaceutical form with enalapril maleate. In this relation, the dissertation presents a modern choice of dosage form, because the orodispersible tablets can overcome problems related to the liquid dosage forms. They can also guarantee the accurate dosing and easy intake. A basic accent in the research is bitter taste masking of the drug through the application of modern approaches such as: the formation of a complex with an appropriate polymer or its encapsulation in polymer microparticles. In addition, in order to obtain the required fast disintegration of the tablets, there were created and characterized alternative disintegrants of natural origin (flax and quince seeds), which can be effective and safe in low concentration.

Knowledge of the problem

The doctoral student describes the main problems and challenges in the development of an appropriate peroral dosage form with enalapril maleate for antihypertensive children's therapy. On the base of 165 literature sources, it was made a thorough literature review describing in details the problems of taste masking of pediatric dosage forms and approaches for its evaluation. A special attention was paid to the existing dosage forms with enalapril maleate and the advantages of enalapril incorporation in taste corrected orodispersible tablets for children's therapy. Except for their taste correction, the tablets should have appropriate biopharmaceutical properties. In this relation, disintegrants were examined in details, playing the role of excipients and securing the required fast disintegration of tablets in mouth. There were discussed the main methods for taste evaluation and it was described the existing variability of the results in pediatrics. In this relation, there were implemented *in vitro* and *in vivo* methods for taste evaluation of the tablet models developed in the dissertation work.

Research methodology

A wide range of methods were included in the dissertation such as:

- development and validation of UV-spectrophotometric method for quantitative determination of enalapril maleate;
- obtainment of taste masked particles with enalapril maleate – formation of complexes of enalapril maleate with Eudragit EPO through precipitation or encapsulation in polymer microspheres through emulsion technique or spray drying;
- characterization of the obtained particle models with enalapril maleate regarding yield, drug loading, shape and size of particles, moisture content, physical state of the drug, interactions with carriers, etc.;
- evaluation of the extent of bitter taste masking of enalapril maleate via *in vitro* examination in artificial fluids, as well as via testing with experimental animals and healthy volunteers;
- obtainment of dry extracts containing polysaccharides from flax or quince seeds aiming to use them as disintegrants in tablets;
- characterization of dry extracts regarding yield, shape and size of the particles, moisture content, loss on drying, swelling index and rheological parameters (angle of repose, Hausner ratio and Carr's index);

- preparation of orodispersible tablets containing polymer microparticles loaded with ealapril maleate and the obtained extracts as disintegrants;
- characterization of the tablets – uniformity of mass, mechanical strength, friability, disintegration, *in vitro* release of enalapril maleate from the orodispersible tablets, taste evaluation of the orodispersible tablets by healthy volunteers, etc.

Characterization and evaluation of the dissertation work

The dissertation work is written in 140 pages and consists of the following parts: introduction, literature review, aim and tasks, materials and methods, results and discussion, conclusions, contributions and references. It is illustrated with 49 figures and 35 tables, which clearly present the received results. The chapter "Literature Review" includes detailed description of the problems with pediatric peroral dosage forms, more specifically taste correction, as well as modern methods for its obtainment and assessment. The "Aim and Tasks" are well structured and argued. "Materials and Methods" section contains full description of the considerably great number of used methods. In "Results and Discussion" section there are presented and discussed the received results, namely taste masking of enalapril maleate through polymer complexes or microparticles, optimization for obtaining dry extracts from flax and quince seeds and assessment of their properties as disintegrants, preparation and characterization of orodispersible tablets. The sections "Conclusions" and "Contributions" include and completely reflect the observed dependences and achievements.

In conclusion, the dissertation work represents one exclusively well considered and performed development, which covers problems such as: the bitter taste masking of the drug, the obtainment of dry plant extracts (containing polysaccharides) as potential disintegrants in a tablet form, the preparation of a model of a pediatric dosage form – orodispersible tablets with appropriate organoleptic and biopharmaceutical properties.

Contributions and significance of the dissertation to science and practice

The main achievements from the performed research studies can be systemized in the following contributions:

- detailed examination and evaluation of the possibilities of Eudragit EPO® to be used for taste masking of enalapril maleate through the formation of a complex with the drug or its inclusion in microparticles;

- developing a method for obtainment of microparticles by spray drying with the use of Eudragit EPO® in water carrier (0,1 M HCl), which excludes the use of organic solvents /vehicles/;

- first time reception of optimal parameters for the obtainment of dry extracts containing polysaccharides from flax and quince seeds through spray drying; proving their potential as disintegrants in orodispersible tablets;

- development of a perspective model of taste corrected orodispersible tablets for pediatric practice with microencapsulated in Eudragit EPO® enalapril maleate and dry extract from flax seeds as a disintegrant.

Assessment of the publications related to the dissertation work

Four publications, related to the dissertation thesis, have been presented (one in a journal with impact factor 1.198), in which Yana Gvozdeva is a leading author. She participated in 12 (twelve) scientific forums. The paper in "Proceedings of the competition *Science and Youth*" discusses the development and validation of UV-spectrophotometric method for quantitative determination of enalapril maleate in different media, which is one of the tasks in the dissertation. The research papers in "Folia Medica" and "Die Pharmazie - An International Journal of Pharmaceutical Sciences" describe the study results related to taste masking of enalapril maleate through the formation of complexes with Eudragit EPO and its encapsulation in microparticles constructed from the same polymer. The paper in "Scientific Research of the Union of Scientists Plovdiv" presents the obtainment of dry extract form flax seeds and its characterization in order to be used as disintegrant in a tablet dosage form.

Two of the research papers related to the dissertation work were cited as follows: the paper in "Folia Medica" was cited in "Romanian Journal of Pharmaceutical Practice" and "Folia Medica", and the paper in "Die Pharmazie - An International Journal of Pharmaceutical Sciences" was cited in "Drying Technology".

The total number of points in this group of indicators (group G) is 37.5, which exceeds the minimum required points (30 points according to the Act for Development of the Academic Staff in the Republic of Bulgaria) for acquiring the educational and scientific degree "Doctor", field of higher education 7. Healthcare and Sport, professional area 7.3. Pharmacy.

Personal contribution of the doctoral student

Undoubtedly, the doctoral student has personal participation and contribution in working out models, data receiving and processing, which is obvious from the presented scientific publications and the participation in 5 scientific projects within a period of 6 years.

Summary of the dissertation

The summary of the dissertation is 64 pages. It accurately reflects the dissertation content. The summary includes the aim and tasks, the applied methods, the main study results (presented in 28 figures and 21 tables), the conclusions and contributions.

Critical notes and recommendations

I have no critical notes. I would like to recommend the doctoral student to publish the interesting results related to the optimization of orodispersible tablet composition.

CONCLUSION

The dissertation work includes scientific and scientific-applied results, which are original contributions and are in conformity with ADASRB, the Regulations for Application of ADASRB and the Regulations of MU-Plovdiv. The doctoral student possesses in-depth knowledge and professional skills in the scientific specialty "Pharmaceutical Technology and Biopharmacy", as well as the necessary qualities for individual implementation of research studies.

Taking into account the relevance of the dissertation work, the adequately planned studies, the modern methods and thorough result discussion, I am fully convinced to give my positive assessment of the dissertation entitled "Approaches for Taste Masking of Enalapril Maleate in Orodispersible Tablets for Pediatric Practice", the summary of dissertation, the conclusions and contributions. I **propose to the honorable scientific panel to award Yana Zhekova Gvozdeva, Master of Pharmacy, the educational and scientific degree Doctor** in the doctoral program "Pharmaceutical Technology and Biopharmacy".

21. 05. 2021 Reviewer:

Sofia Prof. KrassimiraYoncheva, PhD, Doctor of Pharmaceutical Sciences