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REVIEW

by Associate Professor Stefka Nikolova Ivanova-Titeva, Ph.D.
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on 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 doctoral studies: independent study form

Department: "Pharmaceutical Sciences"

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 set of materials presented by the doctoral student on paper and electronic media is in accordance with Section I, Art. 70 (1) of the Regulations for Academic Development at the Medical University of Plovdiv, 2021 and includes the required documents.

The enclosed documents certify the compliance of the doctoral student's education with the requirements of the Law on the Development of The Academic Staff in The Republic of Bulgaria and the Regulations of MU-Plovdiv. They confirm the personal contribution of the doctoral student in the development and publication of the results.
In relevance to the dissertation we enclose 4 publications and 12 participations in scientific forums.

2. Concise biographical data about the doctoral student

Yana Zhekova Gvozdeva was born on February 14, 1990. In 2009 she graduated from a language high school with a profile in German language in Plovdiv, and in 2015 she obtained a degree in Pharmacy from the Faculty of Pharmacy at the Medical University - Plovdiv. The same year, after successfully passing the exam, she was appointed an assistant in Pharmaceutical Technology and Biopharmacy at the Faculty of Pharmacy at the Medical University of Plovdiv. In 2020 she acquired a specialty in Pharmaceutical Technology and Biopharmacy. In February 2019 she was enrolled as a doctoral student in an independent doctoral program "Technology of Pharmaceutical Forms and Biopharmacy" with the topic of the dissertation: "Approaches for Taste Masking of Enalapril Maleate in Orodispersible Tablets for Pediatric Practice".

The doctoral student actively participates in the teaching and research activities of the department, takes part in the development of research projects, training seminars, carries out mobility under the Erasmus Program, participates in conferences, etc.

She has good organizational skills, excellent computer literacy, handles written and spoken English and German.

3. Relevance of the topic and expediency of the set aims and objectives

The presented dissertation of Assistant Prof. Yana Zhekova Gvozdeva is dedicated to one of the current and unresolved problems in the technological practice related to the development of oral medication dosage forms suitable for pediatric practice. The aim of the dissertation, development and characterization of orodispersible tablets with enalapril maleate with improved taste is aimed at solving common difficulties in geriatrics and pediatrics related to swallowing and not always having the opportunity to achieve a well-disguised taste and smell of drugs. The chosen technological approach to obtain orodispersible tablets, a relatively new group of tablet dosage form, which aims in addition to improved patient compliance, to significantly increase the solubility, absorption, bio-availability and clinical effect of the drug in comparison with the conventional dosage forms, undoubtedly determines the scientific and practical contribution of the developed topic. Based on the set aim, the tasks of the dissertation are specified precisely and clearly. On the basis of an extensive written sources review, including specific information about the current level and new research solutions in the technology of orodispersible tablets, the tasks of the dissertation are correctly derived, aimed at fulfilling the purpose: exploring the possibilities for maximum concealment of the bitter taste of enalapril maleate using physico-chemical and technological methods - incorporation of enalapril maleate in polymer complexes by precipitation method and in polymer microparticles obtained by emulsion technique with solvent evaporation and spray drying, structural-morphological and physico-chemical models assessment of the degree of masking of the bitter taste of enalapril maleate by *in vitro* testing in artificial media and testing on experimental animals and healthy volunteers, production of polysaccharides from natural sources – flax seeds and quince seeds for use as disintegrating excipients in orodispersible tablets, development of models of orodispersible tablets with maximally masked bitter taste of enalapril maleate, development and validation of a UV-spectrophotometric method for quantification of enalapril maleate for the purposes of experimental studies.

3. Knowledge of the problem

The doctoral student is well acquainted with the problem, both the facts known in science and the unsolved problems. Furthermore, the aim and tasks are set accurately and an analytical and comprehensive overview is clearly presented, which features adequately the level of problem to be solved. The theoretical overview of the dissertation in a logical sequence and very good interpretation of the written data based on 165 literature sources discusses the therapeutic and technological aspects of the choice of dosage form for children and the possibility of incorporating enalapril maleate in orally dispersible tablets as a suitable dosage form for children's practice. A detailed analysis of the methods for preparing orodispersible tablets has been made, with special emphasis on the use of natural polysaccharides as superdisintegrants. A critical analysis of the most commonly used technological methods and approaches for masking the bitter taste of drugs in orodispersible tablets and of the methods for taste evaluation has been made.

4. Research methodology

Aiming at solving the set purpose and tasks, the doctoral student uses a large set of precisely selected modern spectral and physicochemical methods. A UV-spectrophotometric method for quantitative analysis of enalapril maleate in conditions of artificial gastric fluid with pH 1.2 and in conditions of artificial saliva - buffer with pH 6.8 was developed and validated. The technological conditions of the used methods for masking the taste of enalapril maleate are precisely defined: method of precipitation, method of emulsion technique with evaporation of the solvent and method of spray drying. Using optical and scanning electron microscopy, Beckman coulter particle size analyzer, infrared spectrophotometry, X-ray powder diffractometry, differential thermal and thermogravimetric analysis, the technological characteristics of the obtained polymer microparticles were determined: yield, loading and encapsulation efficiency, shape and morphology of the particles, mean size and particle size distribution, moisture content. Studies have been performed to determine the possible chemical interaction between the drug and the excipients used, the physical condition of the drug in the polymer particles has been determined. Using the set of *in vitro* and *in vivo* methods used, a complex evaluation of the taste of enalapril maleate polymer particles was performed, used as a basis for selecting the most appropriate method for masking the bitter taste of enalapril maleate.

In-depth studies have been carried out for the preparation and technological characterization of dry extracts of flax seeds (*Linum usitatissimum, Linaceae, L.)* and quince seeds (*Cydonia oblonga, Rosaceae*) by the method of spray drying in order to use them as superdisintegrants in orodispersible tablets.

The detailed commentaries and the conclusions of the obtained experimental data are impressive. The doctoral student's experience as a result of joint cooperation with the Department of Pharmacology, Toxicology and Pharmacotherapy at the Medical University of Plovdiv and the Institute of Mineralogy and Crystallography of the Bulgarian Academy of Sciences is also a base for the substantiated scientific interpretation of the results. Part of the research was carried out at the Technological Center for Emergency Medicine in Plovdiv.

6. Characteristics and evaluation of the dissertation

Yana Gvozdeva's dissertation is very well structured and includes content, list of abbreviations used, introduction, literature review, aim and tasks, materials and methods, results and discussion, conclusions, scientific contributions and literature sources, list of publications and participations in scientific forums in connection with the dissertation. It occupies a total of 140 pages, which include 49 figures and 35 tables. The bibliography contains 165 literature sources.

The empirical studies were conducted in strict sequence, following the implementation of the tasks and include:

1. Selection of a method for masking the taste of enalapril maleate by including it in drug-polymer complexes. In-depth studies have been conducted to clarify the influence of polymer concentration and preparation methods - precipitation method, emulsion technique with solvent evaporation and spray drying, on the morphological and physico-chemical characteristics of the obtained models of enalapril maleate particles and their maximum objective evaluation in terms of masking the bitter taste of the drug using appropriately selected methods - *in vitro* testing in an environment mimicking artificial saliva and testing on experimental animals and healthy volunteers.

For each of the methods used for the preparation of drug-polymer complexes of enalapril maleate, optimal compositions are derived, characterized by the best taste-masked properties, yield and average particle size.

Regardless of the method used, a change in the physical state of enalapril maleate-polymer particles was found - transition from the crystal structure into an amorphous state.

No chemical interactions have been identified between the drug and the polymer used and the excipients.

Under the conditions of the precipitation method used in the system, Eudragit EPO® polymer and the drug enalapril maleate have been derived. The influence of the polymer-drug ratio on the physico-chemical and technological characteristics of the obtained polymer complexes has been studied. Low values of loading and encapsulation efficiency of enalapril maleate in the polymer complexes have been established, along with a presence of a large amount of free, unbound drug and unsatisfactory taste masking.

In the method of emulsion technique with solvent evaporation with derived optimal composition of the enalapril maleate microparticles: Eudragit EPO®: ethylcellulose (0.2: 0.27: 0.53) despite the high yield of the obtained microparticles and significant improvement of taste masking at higher ethylcellulose content, the obtained low values for the encapsulation efficiency of enalapril maleate in the polymer microparticles, makes them unsuitable for fulfilling the set aim of the dissertation.

In-depth studies have been performed for the preparation of enalapril maleate - Eudragit EPO® - microparticles using the spray drying method, with experimentally established optimal parameters of the drying process. The optimal ratios between polymer and drug for the production of microparticles with a spherical shape, smooth surface, high yield and high encapsulation efficiency were established, with satisfactory values for enalapril maleate loading. The advantage of the spray drying method over the precipitation method and the emulsion solvent evaporation technique has been demonstrated, both in terms of the characteristics of the polymeric microparticles obtained and in terms of taste masking.

Based on the selected method of spray drying, an optimal model of enalapril maleate - Eudragit EPO® microparticles, derived for incorporation in the composition of orodispersible tablets for pediatric practice, was derived.

2. The results of technological studies on the possibilities of using polysaccharides derived from plants as sources of polysaccharides rich in mucous substances - flax seeds (*Linum usitatissimum, Linaceae, L.*) and quince seeds (*Cydonia oblonga, Rosaceae*) as superdisintegrants in orally dispersible tablets are of scientific and practical interest. The conditions and parameters of the spray drying process for obtaining dry extracts of flax seeds and quince seeds are derived and their main technological characteristics are studied - shape, size and particle size distribution, rheological properties, swelling index. Based on the derived optimal compositions of the dry extracts of quince and flax seeds characterized by spherical particles, small size (4.36 μm to 27.41 μm) and high swelling index, the possibility of their use as disintegrants has been proven in orodispersible tablets.

3. In-depth technological studies of the processes of preparation and characterization of models of orodispersible tablets containing optimally derived composition of the drug - polymer microparticles

and dry extracts of flax seeds and quince seeds have been conducted. The influence of the type and concentration of polysaccharides on the disintegration time of the tablets and the related indicators - wetting time of the tablets and water absorption ratio - has been established. Based on comparative results obtained for models of tablets containing reference superdisintegrants - sodium starch glucolate and soy polysaccharide, the optimal technological model of orodispersible tablets with enalapril maleate-polymer microparticles, characterized by well-masked taste and prerequisite for future implementation of the tablet dosage form for children has been derived.

In the Conclusions section of the dissertation, a total of 6 conclusions are formulated, which are logically connected and derive from the conducted research and the obtained results:

1. The developed and validated spectrophotometric method provides accurate and reproducible quantitative analysis of enalapril maleate in enzyme-free artificial salivary fluid (pH 6.8) and enzyme-free artificial gastric fluid (pH 1.2).

2. The drug-polymer complexes of enalapril maleate and Eudragit EPO® obtained by the precipitation method do not show satisfactory masking of the bitter taste regardless of the working ratios between the components, the achieved yields and the particle size.

3. The emulsion solvent evaporation technique is a suitable method for obtaining microparticles with enalapril maleate and Eudragit EPO® with high yields and optimal particle sizes only after the inclusion of a second structuring polymer with a hydrophobic nature - ethylcellulose. Achieved satisfactory taste masking is a result of the low encapsulation efficiency of enalapril maleate in the microparticles.

4. Appropriate parameters have been established for the incorporation of enalapril maleate into Eudragit EPO® microparticles by spray drying. The obtained particles have optimal physicochemical and structural-morphological characteristics, as well as improved taste qualities.

5. Optimal conditions for obtaining dry extracts of quince seeds (*Cydonia oblonga, Rosaceae, Mill.*) and flax seeds (*Linum usitatissimum, Linaceae, L.*) are derived for use as superdisintegrants in the composition of orodispersible tablets.

6. A perspective model of orodispersible tablets with achieved taste masking of enalapril maleate and optimal technological and biopharmaceutical properties is proposed.

7. Contributions and significance of the development for science and practice

The main achievements of the developed dissertation are systematized and summarized very well and can be evaluated as follows:

Scientific and applied contributions:

1. For the first time, the potential of Eudragit EPO® for taste masking of enalapril maleate was studied by the methods: precipitation, emulsion solvent evaporation technique and spray drying.
2. A modified method for spray drying of Eudragit EPO® with an aqueous carrier (0.1 M HCl) is proposed to facilitate the technological process and eliminate the use of organic solvents.

3. For the first time, optimal parameters for obtaining dry extracts containing polysaccharides from flax seeds (Linum usitatissimum, Linaceae, L.) and quince seeds (Cydonia oblonga, Rosaceae, Mill.) were derived by spray drying and their potential as disintegrant in orodispersible tablets was proven.
4. An optimal model of a pediatric dosage form is proposed - orodispersible tablets containing enalapril maleate microencapsulated in Eudragit EPO® and dry flax seeds extract as a superdisintegrant.

8. Evaluation of the publications on the dissertation work

Four publications are presented, which reflect the results of the dissertation. All papers have been published in scientific journals, one of which is Die Pharmazie - International Journal of Pharmaceutical Sciences with **IF = 1.198**. In the presented publications Yana Gvozdeva is the first author, which confirms the personal participation of the doctoral student in the conducted research and its publication.

There are 3 citations noted, 2 of which are in journals referred to in Scopus.

Total number of points for the doctoral student by group of indicators /G/ = 37.5

The minimum required points by group of indicators /G/ for obtaining the scientific degree "Doctor" in area 7. Healthcare and Sport, according to the Act on Development of the Academic Staff in Bulgaria, are 30.

Materials for 12 participations in scientific forums related to the topic of the dissertation were presented, of which 4 at international congresses and conferences, 5 papers were presented at national conferences and 3 reports - at a national congress with international participation.

9. Personal participation of the doctoral student

The conducted researches, the obtained results and the detailed analysis on the basis of which the conclusions and contributions are formulated are the effort and personal merit of the doctoral student.

10. Abstract

The abstract occupies 64 pages, contains 28 figures, 21 tables and has a very good technical layout. In terms of structure and content, it meets the generally accepted requirements and accurately reflects the performed research, the achieved results, the conclusions from them as well as the main contributions.

11. Critical remarks and recommendations

The critical remarks and recommendations on the dissertation have been discussed with the doctoral student in advance and are taken into account.

12. Personal impressions

My personal impressions of assistant Yana Gvozdeva are very good. She is precise and accurate in her work, possesses very good theoretical and practical training and proven creative abilities and prospects for future contributions to the research work.

13. Recommendations for future use of dissertation contributions and results

The development of dosage forms for pediatric practice and the search for rational technological solutions is a challenge, however, at the same time, an opportunity for implementation in pharmaceutical practice of the developed tablet dosage form for children with enalapril maleate - orodispersible tablets. Of interest for future research are also dry extracts of flax and quince seeds, containing a high percentage of mucous substances and their use not only as disintegrants in dispersible tablets in the mouth, but also to obtain polymeric microparticles to mask the taste of drugs.

Conclusion

The dissertation ***contains scientific and applied results, which represent a contribution to science*** and **meet all** the requirements of the Act for the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for application of this act and the respective Regulations of MU - Plovdiv. The presented materials and dissertation results **fully** comply with the specific requirements of MU - Plovdiv.

The scientometric analysis shows that the total number of points of the doctoral student exceeds the minimum required points for acquiring the scientific degree "Doctor" in Area 7. Healthcare and sport, according to Act for the Development of the Academic Staff.

The dissertation work shows that the doctoral student Yana Gvozdeva **possesses** in-depth theoretical knowledge and professional skills in the scientific specialty Pharmaceutical Technology and Biopharmacy by **demonstrating** qualities and skills for independent research activities.

Due to the above, I confidently give my ***positive assessment*** of the research presented by the above peer-reviewed dissertation, abstract, results and contributions and ***propose to the esteemed scientific panel to award the educational and scientific degree 'Doctor'*** of Yana Zhekova Gvozdeva at doctoral program Pharmaceutical Technology and Bio-pharmacy.

25/05/ 2021

Reviewer: .....

(Associate Professor Stefka Titeva, Ph.D.)