

**“VICTOR BABEȘ” UNIVERSITY OF
MEDICINE AND PHARMACY FROM TIMISOARA
DOCTORAL SCHOOL
PHARMACY DOMAIN**



**RESEARCH ON THE OPTIMIZATION OF THE
PHYSICOCHEMICAL AND
BIOPHARMACEUTICAL PROPERTIES OF ACTIVE
SUBSTANCES, WITH THE PURPOSE OF
INCREASING THE BIOAVAILABILITY AND
THERAPEUTIC EFFICACY**

ABSTRACT

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ABSTRACT

The habilitation thesis "*Research on the optimization of the physicochemical and biopharmaceutical properties of active substances, with the purpose of increasing the bioavailability and therapeutic efficacy*" presents in a synthetic way the results of the scientific research activity, carried out after obtaining the scientific title of Doctor of Pharmaceutical Sciences, in the year 2011, within the Faculty of Pharmacy, of the "Carol Davila" University of Medicine and Pharmacy in Bucharest, under the guidance of Professor Dr. Constantin Mircioiu.

The thesis also presents my main academic achievements, professional activity, as well as career development prospects in the didactic, scientific and academic fields, which support my qualification for obtaining the habilitation certificate.

The first chapter of the thesis is dedicated to scientific achievements, highlighting the articles published and indexed in the ISI Web of Science, the works published in abstract, at a number of national and international events, as well as the participation in research projects. The scientific research activity has an impact characterized by a Hirsch index of 16 (according to the Clarivate Web of Science Core Collection database) and a number of 282 citations (not including self-citations), and according to the Scopus database the h-index has value 15. At the time of drafting the qualification thesis, out of the 47 ISI indexed works, I am the main author of 20 articles, and co-author of 27 articles. The cumulative impact factor of the works published as the main author is 28.722. Also, from the total of scientific works published, a number of 13 articles were awarded by UEFISCDI (Executive Unit for Financing Higher Education, Research, Development and Innovation from Romania). From the list of 10 works selected and analyzed within the habilitation thesis, 2 articles are in the Q1 quartile and 5 are in the Q2 quartile. My research activity also materialized by participating in 5 research projects, obtained through competition, in 4 projects I was a member of the research team, and in one I was in charge of the project.

The research areas that I approached, during the postdoctoral period, had an interdisciplinary character, and the first targeted direction continued and developed the research activity from the period of doctoral studies. Considering the fact that most of the failures in the design of new drugs are due to the low solubility of the new molecular entities discovered, the research undertaken focused on the optimization of the

physicochemical properties and the improvement of the biopharmaceutical profile of the pharmaceutical active components, by encapsulation in the cavity of cyclodextrins.

The data from the specialized literature emphasized the fact that cyclodextrins stood out as carrier molecules for the supply of bioactive compounds, having the main advantage of increasing their solubility, stability, and improving their bioavailability, offering the possibility of developing advanced release systems, as a result of formation of inclusion complexes.

Binary mixtures were prepared of some active substances with low solubility in the aqueous medium, as well as some natural compounds with potential pharmacological activity and a series of cyclodextrins (α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, 2-hydroxypropyl β -cyclodextrin, 2-hydroxypropyl- γ -cyclodextrin, methyl β -cyclodextrin and sulfobutylated β -cyclodextrin sodium salt). The intermolecular interactions between the host molecule (cyclodextrin) and the guest molecule (active substance) of the obtained binary mixtures were evaluated by means of instrumental techniques, and the geometry of potential inclusion complexes was realized by molecular modeling studies. For the inclusion complexes formed between itraconazole and cyclodextrins, the antifungal activity was also determined, and the sensitivity was tested by determining the minimum inhibitory concentration. The results of the molecular encapsulation studies proved the formation of the inclusion complexes, highlighting at the same time their good stability and solubility, as well as an improved antifungal effect, in the case of the inclusion complexes with itraconazole.

The second direction of research was represented by compatibility studies between the drug substance and a series of excipients. These studies provide necessary information about the possible interactions of a physical or chemical nature between the active substance-excipients, which can affect the bioavailability and stability of the final formulation, while avoiding the high consumption of raw materials, and on the other hand reducing the time interval, in which an optimized solid dosage form can be obtained.

Screening the compatibility of an active pharmaceutical ingredient (API) with excipients is recognized as one of the mandatory factors underlying the development of new pharmaceutical forms and can be achieved by using analytical methods from the initial stages of preformulation studies contributing significantly to early prediction, monitoring and characterizing incompatibility.

The compatibility studies were carried out on active substances such as: amiodarone, simvastatin, lovastatin, nortriptyline and a series of excipients, with different roles (diluent, binders, disaggregants, glidants, lubricants) in pharmaceutical formulations, and the evaluation of the compatibility of different IFAs and excipients, was carried out using thermal (TG/DTG/HF/DSC) and spectroscopic (UATR FTIR) analytical techniques. These techniques allowed an appropriate selection of excipients compatible with the active substances used in the studies carried out, and the results can be implemented in the pharmaceutical industry, in choosing the optimal conditions for control parameters in each stage of the technological flow, during the development of a new generic pharmaceutical formulation.

The third direction of research was represented by kinetic studies, which occupy a special position in determining the physicochemical properties and stability of analytes, which are subjected to thermal stress.

The kinetic studies were carried out according to the ICTAC 2000 protocol regarding the main decomposition process that takes place in the temperature range 200–300°C, namely using three isoconversion methods, one differential (Friedman) and two integral (Kissinger–Akahira–Sunose and Flynn – Wall–Ozawa).

The kinetic studies focused on the processing of thermoanalytical data obtained at five different heating rates, in order to obtain realistic kinetic parameters, namely the activation energy (E_a), the reaction order (n) and the pre-exponential factor (A), taking into account the fact that evaluating E_a does not imply knowledge of the explicit equation of the conversion function. However, as a limitation, the correct application of the methods only suggests whether the decomposition mechanism consists of complex overlapping or parallel processes, or whether there are reversible reactions. Results obtained by means of kinetic studies, showed an increased thermal stability, in the case of betulonic acid, which can be explained not only by the stability of the triterpenic fragment, but also by the presence of grafted functional groups.

In the case of the study of the two statins, the results obtained by the differential method indicated a multi-step degradation and were not in good agreement with those suggested by the integral methods, which revealed a single-step degradation process. The third kinetic study indicated an average value for the activation energy and a temperature-independent decomposition mechanism in the case of cholesterol.

The recognition of the scientific research activity was materialized by the awarding of the 13 articles by UEFISCDI, by the invitation to be a scientific referent for a number of 30 articles sent for publication in prestigious international and national journals (Pharmaceutics - FI 4.9, Pharmaceuticals - FI 3.7, Cosmetics - FI 3.4, Gels - FI 4.702, Molecules - FI 4.412, Pharmacy - FI 1.433, Antioxidants - FI 6.7, Polymers - FI 4.329, Chemical Papers - FI 2.097, International Journal Molecular Sciences - FI 5.924, Foods - FI 5.2, Fermentation - FI 3.3), as well as by the invitation received from the journal Pharmaceutics (FI 6.525), in 2021, to be an invited Editor, for a special issue (Nanotechnology-Enabled Strategies to Enhance Topical Bioavailability, 3rd Edition), with the theme proposed by the undersigned, which is currently in its third volume -

(https://www.mdpi.com/journal/pharmaceutics/special_issues/9QFUK9F3ZL).

The second chapter is dedicated to academic achievements and the main teaching responsibilities, in which I mentioned my academic career, with the stages of the academic hierarchy obtained through the competition, the teaching activities and the main administrative activities. I participated as a committee member in the admission, license and dissertation exams of the study programs within the Faculty of Pharmacy; as well as as head of room and invigilator, at the residency exam.

In 2012 and 2013, I was part of the working group for the realization of the admission subjects for the national residency exam. I was also a member of the examination committee, at a series of competitions for teaching positions, organized within the Faculty of Pharmacy.

At the level of the Faculty of Pharmacy, I am part of a series of commissions in the interest of education, as president or member, as well as a member of two commissions for drawing up the periodic evaluation file, regarding the institutional evaluation by ARACIS. Over the years I coordinated a number of 70 undergraduate and dissertation theses, and participated in the development of 5 books: 3 as sole author and 2 materials for practical works as co-author. In 14 continuing pharmaceutical education (postgraduate) courses for pharmacists, I was a course lecturer.

In 2012, I obtained the II Prize - for special merits in the didactic activity, as a result of the anonymous votes obtained from the students of the 5th year, of the Faculty of Pharmacy, within the UMFVBT, from Timisoara, in the evaluation of teaching staff.

Starting with the academic year 2023-2024, I have the capacity of residency coordinator, in the specialty Pharmaceutical and Cosmetic Industry, and from the fall of 2024, I also have the capacity of master's coordinator, at the newly established master's program Pharmaceutical Industry.

Chapter three is dedicated to professional activity. I am a graduate of the Faculty of Pharmacy and the master's program Formulation and evaluation of dermatocosmetic products, within the "Victor Babes" University of Medicine and Pharmacy, from Timisoara. I completed my doctoral studies at the Faculty of Pharmacy of the "Carol Davila" University of Medicine and Pharmacy in Bucharest. My professional path followed the stages of professional development: trainee pharmacist (2000), resident pharmacist (2005), specialist pharmacist (2008), primary pharmacist (2023) and pharmacist, respectively chief pharmacist in the community pharmacy and the main responsibilities associated with them.

The last chapter is dedicated to career development perspectives in teaching, scientific and academic terms. In terms of teaching, I plan to write up-to-date materials, apply modern teaching methods, and organize interdisciplinary postgraduate courses.

In the sphere of scientific concerns, I propose to continue the research directions approached so far, to identify and develop new research directions, by expanding the research area; to maintain existing scientific collaborative relationships and to develop other relationships, with international research groups.

Academically, I will focus on building a career and a professional reputation by developing existing skills, but also acquiring new ones, in line with technological and scientific progress.

Finally, the bibliographic references are presented, as well as the list of the 10 representative works in extenso, which support the content of the present habilitation theses.