UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
„CAROL DAVILA" BUCUREŞTI
ŞCOALA DOCTORALĂ
DOMENIUL FARMACIE

RESEARCH ON THE USE OF NEW ACTIVE PHARMACEUTICAL INGREDIENT AND ANALYTICAL METHODS IN THE PHARMACEUTICAL FIELD

SUMMARY OF THE HABILITATION THESIS

CANDIDATE:

Burcea-Dragomiroiu (Burcea) George-Traian-Alexandru, PhD.;

"Carol Davila" University of Medicine and Pharmacy Bucharest

2022

The Habilitation thesis entitled “Research on the Use of New active pharmaceutical ingredients and Analytical Methods in the Pharmaceutical Field” is a synthesis of the most representative research directions approached during the post-doctoral period.

The thesis presents the research activity carried out after the presentation of the doctoral thesis, entitled “Research regarding the physical-chemical methodology of some cephalosporins and anti-inflammatory substances in different combinations”, including the main perspectives of academic, professional and research career development.

Scientific research in the pharmaceutical field has undergone an unprecedented development lately. We are currently witnessing the emergence of new drugs at an alarming rate, which greatly change the medication used in the treatment of many diseases. The introduction into therapy of new pharmaceutical products have brought to the forefront the analytical studies because of the problems those products raise - biopharmaceutical studies, their biotransformation in the body, therapeutic dosage setting, stability problems, toxicity, etc.

The drug quality is a concept that includes and involves several problems whose resolution based on the performed analyses, certifies that the medicine that receives the quality certificate, corresponds in terms of structure, purity and action, to the purpose for which it was prepared and to the current requirements, regarding patient safety.

Knowing the current requirements, demands and trends in the field of drug analysis is a major obligation for those who perform analyses and the analytical results provided must be accurate, precise, correct, therefore highly reliable, because based on them decisions are made in all areas of activity.

Regardless of the area in which procedures, techniques and methods of analysis are applied, the decisions that are made based on the analytical results are also legal in nature, so the analyst has a great legal responsibility, and by that he confers that responsibility to the analytical act. In performing an analysis, the analytical reagent plays an important role, which is the basis of an analytical method that facilitates that chemical analysis.

The use of organic reagents has led to the development of new methods of analysis which also benefited from the field of physical-chemical control of the drug. A newly created analytical method must be validated, and the validation methodology applied is meant to demonstrate that the proposed method corresponds to the intended use. Statistical processing of the results of an analysis offers the possibility to obtain the most probable value that is as close to reality as possible.

The analysis methods presented have been validated in accordance with conventional regulations, such as those of the Food and Drug Administration (FDA), European Medicines Agency (EMEA) and International Conference of Harmonization (ICH).

An important problem in pharmaceutical research is the optimization of the bioavailability of substances with low solubility and high permeability of the second class of biopharmaceuticals, which can be achieved through various methods such as complexation with carbohydrate derivatives such as cyclodextrins when inclusion complexes are obtained,

encapsulation in lipo- or water-soluble systems for administration and transport or formulation in oral pharmaceutical forms with modified release.

The Habilitation thesis is structured into three sections. The first one describes the personal, professional and academic achievements, the second section is presented in the form of a detailed presentation of the main scientific achievements after the doctoral dissertation, and the third section presents the main future plans regarding the evolution and development of the professional, scientific and academic profile.

In the chapter entitled ”Professional and Academic Achievements” I presented the entire academic and professional career during my 20 years of activity at the Faculty of Pharmacy of the ”Carol Davila” University of Medicine and Pharmacy - Bucharest, and in 2012 I defended the PhD thesis in the field of Pharmaceutical Sciences. Also during this period, I passed the exams for obtaining the academic titles and various degrees specific to the profession of pharmacist: resident, specialist, mayor. Professional training has been one of my main concerns with a multidisciplinary educational path adapted to the nature of the subjects taught. Throughout this period, I have been concerned with motivating and supporting pharmacy students to deepen the scope of the drugs quality control. In this regard, I have helped, first of all, to improve the didactic material. Thus, as a co-author, I have participated in the development of 2 Laboratory Books required for pharmaceutical practical applications in the field of drug control. I have also been involved in the development of the didactic material - support for the Drug Control courses. The aspect of professional pharmaceutical activity completes, necessarily and elegantly, the academic and scientific activity. To that end, I have informed, prepared and supported numerous training courses and continuous training for pharmacists across the country. I have also participated, as a member of the Scientific Council and Organising Committee, in organizing numerous events within the Romanian pharmaceutical community.

Another aspect I would like to highlight relates to a special field of activity, which I have voluntarily assumed, through the involvement in the activity of Managing Editor at Farmacia journal, the only publication in the Romanian pharmaceutical scientific field indexed and quoted on the basis of ISI Thomson Reuters data (IF / 2021 = 1.550).

In the second chapter of the thesis, entitled ”Scientific Achievements”, I have detailed the results obtained and published in the form of articles quoted ISI or indexed by BDIs, as well as in books / chapters of books published nationally or internationally.

The main research directions developed in the scientific field are in line with the Development Plan of the faculty, the university and respectively the Research and Development-innovation strategies elaborated at national and international levels and can be grouped as follows:

- ✓ Novel research regarding the development and validation of new analytical methods used in drug control
- ✓ Experimental research for the evaluation of the pharmacokinetic profile for several compounds

- ✓ The mechanisms of action - therapeutic effects - adjuvant therapy inter-relationship in *in vitro* studies
- ✓ Applied research in the microbiology field

Within the first research approach I have conducted several analyses, by using HPLC, TLC and spectrometry method for establishing the quality of several pharmaceutical products. For the development of the chromatographic method for piroxicam, a design of experiments (DOE) approach was used, along with a Box-Behnken design in order to identify the significant parameters for the optimization, by simultaneously taking retention time, peak symmetry, resolution of the chromatographic separation, number of theoretical plates and capacity factor of the first eluting peak as responses. The validation, where was performed, was carried out in accordance with the current ICH guidelines in terms of specificity, linearity, precision, accuracy, limits of detection/quantitation, and system suitability.

The second research direction's main focus was the in vitro dissolution data indicating meaningful change or discrimination when there is a change in critical material attributes and critical product information. In this regard, six pharmaceutical dosage forms (sugar coated tablets, hard and soft gelatin capsules, oral suspension and rectal suppositories), containing various strengths of ibuprofen as single active ingredient, were evaluated *in vitro*, based on the available compendial recommendations. I presented also the results of *in-vitro* release tests applied for assessing the impact of mechanical splitting on the performance of sustained release oral solid formulations containing metoprolol succinate and for underlying the influence of ethanol content in acidic media on the *in vitro* release of tramadol hydrochloride from controlled release tablets.

The third chapter's main focus is correlated with the purpose of finding new cancer treatments. For this, it was to evaluate the potential effects that the association of silymarin and capsaicin could induce in HT-29 colorectal adenocarcinoma cells, with the goal of investigating the cell viability, cell morphology as well as the DNA fragmentation as a result of apoptosis. Also, the research aimed to develop a circulating colorectal tumour cells detection protocol by using flow cytometry, by comparing the outcomes of the positive and negative selection strategies after fluorescent staining with the appropriate antibodies and flow cytometry analysis of the samples.

For the fourth direction, I emphasised the important role of the pharmacist in preventing oral diseases and in preserving healthcare. Pharmacists are experts in the field of drugs and they use their clinical expertise and practical knowledge to ensure the safe supply and use of medicines to the general population.

The last chapter of the thesis presents the main future plans for the evolution and development of the professional, scientific and academic profile. The academics must have the ability to tirelessly combine teaching and scientific research, giving equal weight to them. The results achieved both in didactic and research activity are innovative and ensure the observance of the fundamental principles of quality assurance in the national and European space of research and higher education.

On the principle of continuity, I wish to build my professional profile in the coming years. In this respect, I intend to improve (in fact periodically update) the experimental methodology in the practical work with the students as a result of the acquisition of modern equipment, based on the ongoing and future research contracts of the discipline. I propose developing and introducing new experimental works within the Drug Control Laboratory. These new protocols will be modern, aligned with laboratory homologous curricula in the countries of the European Union.

As far as the development of scientific research activity is concerned, I ~~have~~ proposed that it should be oriented mainly on the same research directions in which I have achieved significant results, but I will also consider the development of related directions. The objectives of the research activities are to increase its competitiveness, to develop partnerships in the priority areas for the design of new technologies, innovative products and implementation mechanisms to solve complex problems associated with the research areas, and to disseminate the results of the studies accordingly.

In conclusion, the main objective of my career was, is and will be that of professional self-refurbishment so that it can carry out educational and research activities at a high-quality level, respecting both its own principles, and the qualitative and ethical ones adopted by the Charter and the Strategic Plan of UMF “Carol Davila” Bucharest.