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MEDICINE AND PHARMACY TIMIŞOARA
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PHARMACY DOMAIN

MODULATION OF PHYSICOCHEMICAL AND BIOPHARMACEUTICAL CHARACTERISTICS OF DRUGS AND UNCOVERING NEW PHARMACOLOGICAL PROPERTIES

ABSTRACT

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THESIS ABSTRACT

The habillitation thesis ”Modulation of physicochemical and biopharmaceutical characteristics of drugs and uncovering new pharmacological properties” presents synthetically my scientific and academic research results obtained after defending my PhD thesis at ”Iuliu Haţieganu” University of Medicine and Pharmacy” in Cluj-Napoca, with Professor Marius Bojiţă PhD as scientific advisor. My PhD thesis was rated *excellent.* The thesis also presents my main academic, scientific and professional achievements and includes a plan of development for my acadmic career. It is a proof that qualifies me for the habillitation degree.

This thesis is divided into four sections.

My activity of scientific research which I carried out after acquiring the PhD in Pharmacy has followed three main interconnected research directions, presented in the first section of this thesis along with significant results and important scientific achievements.

My first research direction had as a starting point the challenge that pharmaceutical industry has been faced with for the last two decades, i.e. poor solubility with unfavorable implications for bioavailability in about 90% of the developmental pipeline drugs and in 40% of approved drugs. Within this framework, using and developing my skills and knowledge acquired during the doctoral studies, this research direction aimed at improving the physicochemical properties and biopharmaceutical profile of some drug substances by encapsulation in cyclodextrins, their ability to enhance the solubility, dissolution and bioavailability of drugs, as a result of inclusion complexes formation being a known fact. The inclusion complexes of some poorly soluble drugs with natural cyclodextrins such as β-cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD) and derivative cyclodextrin with enhanced solubility, such as 2-hydroxypropyl-β-CD, 2-hydroxypropyl-γ-CD, random methyl-β-CD, heptakis(2,6-di-O-methyl)-β-CD and heptakis(2,3,6-tri-O-methyl)-β-CD have been obtained and characterized using thermal analysis and spectroscopic methods. The geometry of the inclusion complexes and the bond types which were formed between host and guest molecules have been analysed using molecular modeling. Job’s method, Benesi-Hildebrand technique and phase solubility studies were employed for the characterization of inclusion complexes in solution. Also, the

solubility profile of inclusion complexes was assessed using the saturation solubility studies by comparison with the parent substances. The results revealed the encapsulation of drug substances in cyclodextrins cavity and also the solubilising effect of cyclodextrins that leads to improved biopharmaceutical features of the studied pharmaceutical substances.

The second research direction is represented by the compatibility studies with excipients. The selection of suitable excipients in drug development process is of major importance for the efficiency, quality, safety and stability of pharmaceutical dosage forms. The compatibility of two inclusion complexes of antipsychotic drugs with methylated cyclodextrins (selected in order to ensure the best solubility increase of drug substances) with excipients frequently used in pharmaceutical formulation was assessed by means of thermoanalitical methods, FTIR spectroscopy, powder X-ray diffractometry which allow to select the excipients compatible with the inclusion complexes. The results obtained in this research direction also revealed the stabilizing effect of cyclodextrin by preventing the drug-excipient interaction as a result of drug encapsulation in cyclodextrin cavity.

The third research direction, having a strong multidisciplinary character aimed at revealing new pharmacological properties for drugs that are already approved by means of complex network science. Starting from the information related to drug-drug interaction from database DrugBank 4.1 and using the complex network science tools (two clustering methods, namely energy model layout and modularity algorithms), a complex network was built (interactome), containing 9 topological communities and 7 modularity classes, similar to social network, where nodes represent drugs and links represent the interactions between drugs. After labeling topological comunities and modularity classes using a pharmacological property common to most, the results of the analysis revealed that 15% of drugs appear to comply with neither topological, nor modularity labels, thus providing assumptions for repositioning, in an appropriate pharmacological property, corresponding either to topological label, or to modularity label.

At the moment of writing my thesis**,** the postdoctoral scientific research activity resulted in the publication of 14 *in extenso* papers in ISI quoted journals, of which 8 in Q2 journals, 7 as main author and one in Q1 journals as classified by Thomson Reuters (Journal of Thermal Analysis and Calorimetry – Q2; Molecules – Q2; Scientific Reports – Q1). The research activity includes, also, an ISI proceedings

paper and 20 abstracts published in volumes of relevant national and international scientific meetings (two in ISI indexed journals). The impact factor for the papers as main author is 20,004. In the postdoctoral period I was and still am involved in two research projects in the scientific area of the habilitation thesis. The recognition of the scientific achievements at national and international levels led to citations which brought about a Hirsch index of 7 according to ISI Web of Science, Core Collection, an invitation to be a reviewer for articles submitted for publication in valuable journals, and also to national awarding for scientific publications.

The next two sections of my habillitation thesis contain aspects of my academic and professional career development. It includes the academic path with all the stages of the academic hierarchy (in 1999, junior assistant professor, Pharmaceutical Chemistry; in 2002, assistant professor in the same discipline; in 2013, lecturer, Drug Analysis, Environmental and Food Chemistry; from 2018, associate professor in the same discipline) and the main responsabilities, activity with students, postgraduate teaching activities along with administrative-managerial activities (Head of Drug Analysis, Environmental and Food Chemistry Discipline since 2015, Head of Department 1 since Dec. 2019). Over the years I was involved in compiling five teaching textbooks (1 as first author) and I supervised 62 Bachelor and Master dissertations.

The third chapter is dedicated to my professional activity. In 1998 I graduated from ”Victor Babeș” University of Medicine and Pharmacy Timișoara, Faculty of Medicine, Pharmacy Specialization, (Valedictorian); I acquired licensure at ”Carol Davila” University of Medicine and Pharmacy București, Master and PhD at ”Iuliu Hațieganu” University of Medicine and Pharmacy Cluj-Napoca. My professional activity as intern pharmacist, specialist and pharmacist manager in the community pharmacy is revealed in this chapter, along with the main associated responsabilities, the professional traineeships and professional grades obtained.

The fourth section is dedicated to future prospects for development at teaching, scientific and professional levels. The results obtained so far encourage me to continue my scientific activity in the above-mentioned research directions, and at the same time, I intend to identify and investigate new research directions in line with the progress of science and technology. In the field of didactic activity, my main concern will be continuously improving of contents and teaching methods, promoting and encouraging lifelong learning.

In the end the main bibliographic references as well as a list of 10 *in extenso* original articles supporting this habillitation thesis are presented.