

THE ABSTRACT OF THE THESIS

Study of cyclodextrin complexes to optimize solubility and development of capillary electrophoresis methods for the analysis of compounds of pharmaceutical interest

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This habilitation thesis summarizes my scientific, professional and academic work carried out after obtaining the Ph.D. in Pharmacy. In 2002, I supported the doctoral thesis entitled "Rectal pharmaceutical forms with benzodiazepines", elaborated under the scientific guidance of Prof. Dr. Adriana Popovici at UMF. Targu Mures.

My didactic, professional and research activities have taken place at the University of Medicine and Pharmacy of Tg. Mures, Faculty of Pharmacy, from 1992 until today, at the discipline of Pharmaceutical Chemistry, Department of Specialty Pharmaceutical Sciences.

The main professional and academic achievements are presented in the first chapter, having as a reference a postdoctoral activity of more than 15 years.

The scientific achievements in this habilitation thesis are covered in three main chapters:

- Study of cyclodextrin complexes with hydrophobic substances in order to optimize bioavailability and physico-chemical stability of active substances;
- Development of capillary electrophoresis methods for the analysis of compounds of pharmaceutical interest;
- Other physicochemical studies applicable in drug analysis.

The experience gained during the elaboration of the PhD thesis - the use of cyclodextrins as auxiliary substances for increased bioavailability of pharmaceutical substances- was also applied in the post-doctoral period. Thus, the main aim of the research was to obtain cyclodextrin inclusion complexes for low aqueous solubility drug substances. Cyclodextrins are cyclic macromolecules whose external hydrophilic surface gives them water-solubility, while the lipophilic inside surface of the molecule, can accommodate non-polar molecules or parts of the molecule with the formation of an inclusion complex. By molecular encapsulation of a drug substance (guest), the physical, chemical and biological properties of the pharmacon can be drastically altered without affecting the intrinsic penetration ability of lipophilic biological membranes and its interaction with biological receptors.

The interaction of azole antimycotics with cyclodextrins has been studied to optimize their bioavailability. Imidazole derivatives are highly hydrophobic substances, a disadvantage for their bioavailability. Investigation of interactions of antimycotic-cyclodextrin complexes, evaluation of complex inclusion characters of the obtained products was performed by nuclear magnetic resonance spectrophotometry, which provides information on complex stability and also suitable for providing precise information on stoichiometry and the steric structure of the inclusion complex. Molecular modeling of complexes has completed the information on the ability to include partially or totally the guest molecule from an energetic point of view in the cyclodextrin internal cavity. In order to characterize the complexes thermal differential scanning calorimetry method and IR spectroscopy were also used.

Another direction of research was the development of capillary electrophoresis methods for the analysis of compounds of pharmaceutical interest.

Capillary electrophoresis is a relatively new technique of separation that is increasingly gaining momentum in the analysis of drug substances, being considered a viable alternative and a method for high performance liquid chromatography (HPLC) techniques; presenting advantages of low consumption of

solvents, reagents and analytes, and also low analytical time, high versatility, increased efficiency and rapid development of the analytical method. This chapter contains three subchapters which encompass the chiral enantiomer separations; simultaneous separations from fixed combinations of drug substances; respectively simultaneous separations of chemically related substances. In the field of chiral drugs there is a close link between the stereochemical characteristics of the molecule and its pharmacological activity. Particular attention is paid to the problem of the separation of enantiomers and to the use in therapy of the enantiomer with maximum efficacy and less side effects / toxicity. The chiral separations were carried out with cyclodextrins, as chiral selectors, for a series of pharmacologically important compounds: fluoxetine, β -blockers, sibutramine etc. In another study, by using Captisol® (sodium salt β -cyclodextrin sulfobutyl ether) as a chiral selector, enantioseparation of nine drug substances from different pharmacological groups has been achieved.

Fixed dose combinations of active substance are commonly used in the treatment of high blood pressure medication. Combinations of telmisartan-amlodipine, telmisartan-hydrochlorothiazide, and also atorvastatin-ezetimibe used in hypercholesterolaemia have been studied.

Within the simultaneous separations of chemically related substances by capillary zone electrophoresis, separation of H1 antihistamines and separation of cephalosporins was achieved.

The last part of the scientific research includes the study of polyoxometalates of pharmacological importance with antibacterial effects, the complexes obtained were characterized by physico-chemical methods (UV, IR, TGA, conductometry, X-rays, antibacterial activity).

The thesis ends with a chapter devoted to future perspectives in the didactic and scientific career followed by conclusions and bibliographical references. In terms of teaching activities, it is important to update and continuously improve the analytical program of practical chemistry courses and works, I intend to modernize the infrastructure, equipments and equipment of the discipline of Pharmacy Chemistry in order to improve the quality of the didactic process; publishing articles in ISI or BDI indexed journals. Academic activity involves engaging in various activities for the benefit of the academic community.

At the scientific level I would like to submit and win grants / projects as project director / member.

The future research directions are the continuation of current research directions: the study of cyclodextrin complexes, the development of new methods of capillary electrophoresis.

A new direction of research is testing the biodegradability of new types of high purity alloys in the Mg-Ca system, applicable in implantology. This research theme will be carried out within the framework of the research grant entitled "Installation for Invented Induction of High Purity Lightweight Bio-Compliant Alloys" PN-III-P2-2.1-PTE-2016-0115-BIOLEV, through electrochemical studies, Thermal analysis.