SUMMARY OF THE HABILITATION THESIS

The habilitation thesis "Complex Physical and Chemical Screening Techniques of Pharmaceutical Interests and Potential Bioactive Compounds" presents synthetically the results of the scientific research activity that I have carried out over the last 6 years, after obtaining the scientific title of Doctor of Exact Sciences - Chemistry in 2011.

Subsequent defending the PhD thesis, the scientific research activity was oriented in three main directions, interconnected, demonstrating a strong inter- and transdisciplinary character. This habilitation thesis is focused on all three directions, namely:

1) Synthesis, physicochemical characterization (spectroscopic techniques and thermal analysis) and screening of the biological activity of new organic synthetic or semi-synthetic compounds, respectively of some metal complexes with transitional ions;

2) Studies of solid-state thermal stability of some active pharmaceutical ingredients or potentially bioactive compounds using classical and isoconversional kinetic methods, with the establishment of the decomposition mechanism;

3) Studies regarding the solid-state compatibility of some active pharmaceutical ingredients with excipients (preformulation studies) using instrumental techniques.

The habilitation thesis is structured in three parts, based on **10 papers that I considered representative** aut of the **78 personal scientific articles published in ISI Web of Science after defending the PhD thesis**: 47 as main author (23 first author and 24 correspondent author) and 31 as co-author.

Part I of the habilitation thesis presents in the three subchapters the main professional, academic and scientific achievements, namely the current scientific context regarding the importance of the approached domains, with reference to personal publications, but also to the numerous studies recently published by other research groups.

The first research direction focused on the synthesis and characterization by complex (physicochemical and biological) screening of new derivatives belonging to the class of heterocycles (1,2,4-triazoles) and triterpenoid semisynthesic compounds, derivatives of betulin – betulonic acid.

Chemistry of 1,2,4-triazoles is considered the research topic that continues the studies undertaken within the doctoral thesis, aiming in particular at optimizing the reaction conditions by which the synthesis of the functionalized products can be made as easy as possible. At the same time, for the synthesized compounds the thermal stability was investigated, following their use as ligands and study of their complexes with transition metals.

The biological activity of the synthesized compounds (both 1,2,4-triazole

derivatives and betulonic acid and its derivatives) was evaluated in two directions - by testing the antiproliferative effect and cytotoxic potential of the compounds, respectively testing the antibacterial activity by using some standardized protocols.

The evaluation of thermal stability in solid-state by employing kinetic methods on thermolysis mechanisms was carried out in an oxidative atmosphere (because most processes involving potentially bioactive substances or active pharmaceutical ingredients are taking place in air), and was performed in accordance with the reccomendations of the International Confederation for Thermal Analysis and Calorimetry (ICTAC) 2000 protocols, which indicate the use of several heating rates and the use of isoconversional methods for the estimation of kinetic triplet. Following these considerations, in the majortiy of our studies, we employed two isoconversional integral methods (Flynn–Wall–Ozawa and Kissinger-Akahira-Sunose) a differential one (Friedman), respectively a fourth method, elaborated by Ramon Serra, Rosa Nomen and Julià Sempere, and later developed by Titus Vlase, Gabriela Vlase and Nicolae Doca, the non-parametric kinetic method, NPK. The main advantages of using the NPK method are that it allows a clear identification and separation of the individual parallel processes occurring in a compound's overall degradation process and that it provides information about the nature of the transformation (a chemical reaction or a physical transition).

Concerning compatibility studies between active pharmaceutical ingredients and excipients, complex physico-chemical screening techniques have gained a leading edge in modern drug technology, being increasingly implemented in preformulation studies, as it provides rapid, reliable and reproducible results. Thus, in the habilitation thesis is presented an example of a preformulation study of the pharmaceutical active compound simvastatin and eight excipients (starch, microcrystalline cellulose, lactose monohydrate, polyvinylpyrrolidone, colloidal silica, talc, magnesium citrate and sorbitol) frequently used in the solid formulations, with various roles in the final formulation. By corrobation of the results obtained by complex physico-chemical screening, such as thermogravimetric and differential thermogravimetric analysis, heat flux analysis, Fourier transform infrared spectroscopy and powder X-ray diffraction, the incompatiblilty of the active pharmaceutical ingrediend with some excipients was revealed.

Part II of the habilitation thesis presents in the two subchapters the plans for evolution and development of the professional and scientific career, respectively of the academic one.

Part III of the habilitation thesis presents the list of the 309 bibliographic references consulted.