The important challenge of the modern pharmaceutical industry is to improve the solubility and bioavailability of Active Pharmaceutical Ingredients (APIs), especially those belonging to II and IV groups of Biopharmaceutical Classification System (BCS). As a standard, they are produced in the crystalline form characterized by a periodic arrangement of molecules in all three spatial dimensions. In such form, they are very stable and easy to store, but at the same time, many of them are less water-soluble and bioavailable (hence relatively high doses are needed to achieve the desired therapeutic effect). In this context, the production of amorphous - molecularly disordered APIs, which in many cases are characterized by much better solubility, higher reactivity and enhanced tableting properties than their crystalline counterparts, seems to be a perfect solution. Unfortunately, a high physico-chemical instability of these systems, manifested by a tendency to recrystallization, isomerization, or chemical degradation (due to variation of temperature, moisture, pressure, etc.), prevents their long-term storage and, consequently, large-scale implementation on the market.

Despite many years of research performed by different groups around the world, considering the influence of production methods/conditions, thermodynamic factors, molecular dynamics, and intermolecular interactions on the functional properties of amorphous pharmaceuticals, it was not possible to develop models and mechanisms explaining their physical and chemical (in)stability in a comprehensive manner. One of the reasons for this is the neglect of the role of the internal structure, which is a key factor in determining the thermodynamics, mobility of molecules and, consequently, stability as well as solubility. The structure of amorphous APIs is often incorrectly considered to be completely disordered. It turns out, however, that many APIs, e.g., ibuprofen, flurbiprofen, celecoxib, ritonavir, itraconazole, terconazole, vitamin A, folic acid, can form various types of supramolecular structures, liquid-/plastic-/meso- or nano-crystalline domains, which, at first sight, appear to be devoid of any molecular organization. In consequence, the meso-/nanoscale molecular association and ordering phenomena are usually overlooked in the discussion on the properties of amorphous pharmaceuticals. Therefore, the main goal of this project is to characterize in detail the internal structure of APIs forming different types of supramolecular domains and non-crystalline phases, produced by several methods (vitrification, compression, milling) and subjected to external conditions (temperature, pressure) simulating the production processes. We are going to fill the gap in the current state of knowledge on the correlations between the manufacturing conditions and the structure of non-crystalline pharmaceuticals, their molecular dynamics and thermodynamics, and as a result to predict the physico-chemical stability of these systems, the ability to form various crystal phases (polymorphs) and solubility.

We plan to use mainly two experimental techniques for characterization of the neat APIs as well as their mixtures with low- and high-molecular-weight excipients (EXCs), namely Broadband Dielectric Spectroscopy (BDS) and X-ray Diffraction (XRD) in the wide-angle range. We are also going to carry out pioneering high-pressure investigations using both methods. It should be mentioned that BDS and XRD have been proven so far to be the most useful and informative tools in discovering and monitoring the static and dynamical properties of supramolecular associates in many systems, e.g., alcohols. BDS allows probing the molecular mobility, the global and local relaxation processes and provides an indirect view of the size and architecture of supramolecular clusters. On the other hand, XRD gives a direct fingerprint of the atomic/molecular-level structure. In this project, we will take advantage of current synchrotron methods and perform breakthrough high-pressure XRD measurements allowing us to characterize the short-, medium- and long-range intermolecular structure of APIs. Moreover, the application of a revolutionary pair distribution function and computer modeling will facilitate the interpretation of experimental data and allow the creation of models of the molecular organization in the studied APIs. By combining the results of BDS and XRD studies with outcomes of calorimetric, infrared and Raman spectroscopy measurements, it will be possible to discover the genesis of the properties of APIs forming supramolecular clusters. In addition, we will explain the impact of the preparation route (vitrification, compression, milling) as well as the thermal and pressure history of the sample on the internal structure and related properties, including physico-chemical stability and solubility.

The unique set of data obtained from so wide-array of methods, including pioneering high-pressure measurements, will allow us to address fundamental issues related to the formation of the supramolecular meso-/nanoassociates in neat APIs and API-EXC binary mixtures produced via different routes simulating the production processes. Moreover, except for the obvious scientific value of the proposal, our results can serve as a base to prepare new, more efficient pharmaceutical formulations of controlled stability and dissolution rate. In the long run and wide perspective, this project may be of great importance for more effective treatment of civilization diseases with fewer side effects.