One of the key challenges of modern pharmaceutical industry is to improve the solubility and bioavailability of already existing drug substances, especially those categorized as class II and IV according to the Biopharmaceutics Classification System (BCS). In this context, amorphous pharmaceutical ingredients (APIs), which in most cases are characterized by much better solubility and higher reactivity in comparison to their crystalline (traditional) counterparts, seem to be the perfect solution. Unfortunately, a large physical instability of these systems prevents their implementation on the market. Results of recent papers have shown that by preparing API-polymer (or saccharide) molecular dispersions the stability of amorphous active substances can be significantly improved. One can add that such excipients may inhibit crystallization or sometimes even chemical degradation of APIs. However, it should be noted that most of research on this type of systems is carried out under atmospheric pressure, without taking into account the effects of compression, which is an inherent part of the formulation process (solid dosage forms). This is particularly surprising in the context of the latest, still very rare reports clearly demonstrating that under high pressure uncontrolled isomerizations of pharmaceuticals or phase transitions associated with crystallization, transformation between different polymorphic forms, which affect the safety and efficacy of amorphous final product, can occur. A prime example is carbamazepine, for which the transition of one polymorphic form into another, having different properties of bioavailability and reactivity, led to the withdrawal of the drug from the market. It should be emphasized that one-component systems are very rare in the pharmaceutical formulations. These are usually multi-component preparations in which the molecules of different substances interact with each other with various strength. Therefore, it seems necessary to perform similar studies at different temperature and pressure conditions on at least binary systems to learn more about the impact of environment, molecular packing and intermolecular interactions on the physicochemical stability, kinetics of phase transitions, growth and morphology of the obtained crystals.

Within this project we plan systematic research of molecular dynamics and physico-chemical properties of binary systems composed of active substance (from II or IV Class of BCS) and modified (cyclic, substituted, ionic) carbohydrate at different thermodynamic conditions. One of the key threads of our measurements will be confirmation of the homogeneity of molecular dispersions, having a significant impact on their physical stability. Another very important theme will be verification, how intermolecular interactions affect the kinetics of API crystallization from binary mixtures. For this purpose, we intend to use carbohydrates with altered chemical structures, influencing the nature of intermolecular interactions in the sample. It is extremely interesting, especially that the classical nucleation theory (CNT) does not take this problem into account. Moreover, we will also study the kinetics of polymorphic transformations and possibility of obtaining crystals with new crystal lattice structures, which cannot be produced under atmospheric pressure. Another issue will be examination the effect of environment and thermodynamic conditions on the growth rate and morphology of obtained crystals. We are also planning extensive research to answer the question how the change in the composition, modification of pressure and temperature will affect the aging process in API-modified saccharide mixtures and consequently the physical stability of studied systems. At the end, we would like to see what will be the impact of carbohydrate matrix on the chemical interconversion of APIs. It is worth mentioning that investigations on the saccharides clearly showed, that by varying the polarity of the medium one can significantly change the distribution of isomers and slow down or speed up the reaction.

The main technique used for studies performed at atmospheric (p=0.1 MPa) and elevated pressure (up to 600 MPa) will be broadband dielectric spectroscopy. Moreover, we also plan to carry out additional measurements using: X-ray diffraction, differential scanning calorimetry (DSC), infrared (IR) and Raman spectroscopies, optical microscopy, as well as theoretical (DFT) calculations. They will allow us to get more information about phase transitions, the homogeneity of samples, intermolecular interactions, kinetics of isomerization, crystallization etc. In addition, we are going to perform solubility studies of API-modified saccharide binary mixtures in different media (e. g. water, 0.1 M HCl, phosphate and acetate buffers).

We are convinced that results of our research will go well beyond the current state of art and contribute to a better understanding of the fundamental issues of pharmacy and physicochemistry of condensed matter. We assume that they will allow us to better understand the factors affecting the physical and chemical stability of investigated systems. This will result in the development of new formulations of existing active substances, characterized by improved bioavailability and low toxicity.