Cardiovascular disease (CVD) is a disorder of the heart and blood vessels. CVDs are the main cause of death and disability in Europe. Despite the advances in CVDs interventions and a wide variety of drugs, this condition is still not adequately controlled in many patients. Key reason for this is a number of different tablets that must be taken by the patient, resulting in non-adherence. Combining drugs with synergistic mechanisms of action in one dosage form (fixed-dose combination, FDC has potential benefits such as improved efficacy, reduced dosing, lower cost or enhanced patient compliance. A typical pharmacotherapy is based on solid dosage formulations (i.e. tablets or capsules) where solid active pharmaceutical ingredients (APIs) are used. The APIs formulated into solid dosage forms following oral administration must dissolve in gastrointestinal tract and penetrate biological membranes in order to be pharmacologically active. However, about 40% of currently marketed pharmaceutical molecules and around 75% of newly synthetized active substances exhibit significant aqueous solubility issue. Poor solubility and low dissolution rate often lead to poor bioavailability and therefore might lead to pharmacotherapy failure. Therefore pharmaceutical technologists focus efforts to improve the limited bioavailability of API by increasing the aqueous solubility and in effect the dissolution rate. There is a clear demand for an effective way to increase the dissolution rate of poorly soluble APIs.

A solid API used in a solid dosage form can exist in crystalline (ordered, stable) or amorphous state (disordered, unstable). Therefore, amorphous APIs exhibit usually better dissolution rate and hence have been used for the development of poorly soluble API to promote therapeutic activity. As the amorphous state is a high-energy state those amorphous solids exhibit impaired stability due to tendency to reorganization into more ordered, more stable form, by a process of recrystallization or devitrification. This is the major cause hindering its applicability in drug production.

Up to date, the first line stabilization method of amorphous APIs has been formation of polymeric amorphous solid dispersions (PASDs). In PASD the improved stability is achieved by entrapping API in a high energy glassy state between the polymer chains. However, development of PASD faces many practical challenges and thus other methods of stabilisations are being investigated. Recently, there has been considerably significant interest expressed by both academia and industry in regard to improving dissolution rate and stability of APIs by combining amorphous drugs into one single-phase system called co-amorphous system. It has been demonstrated that the use of co-amorphous systems improves physical stability, dissolution rate and bioavailability. The co amorphous systems development is still at its infancy stage and therefore little is known about the molecular mechanism of improved stability and dissolution rate and further research in this area is required.

The aim of this project is to obtain novel, pharmacologically relevant API-API co-amorphous systems of poorly soluble drugs with optimized solubility and stability properties. The primary goal of this project is focused on the investigation how to stabilise amorphous active pharmaceutical ingredients throughout formation of the co-amorphous systems and on understanding the mechanism of the stabilisation and its impact on the dissolution behaviour. To evaluate the impact of the preparation method and the storage conditions on the physicochemical properties of the co-amorphous systems, the materials will be obtained by different methods and will undergo physical ageing in different temperature, time and relative humidity conditions. Materials will be comprehensively characterized by main analytical methods i.e.: Differential Scanning Calorimetry, X-ray Powder Diffraction and Fourier-Transform Infrared spectroscopy. Dissolution tests will be applied to assess the influence of co-amorphization on dissolution profiles of examined APIs. Furthermore, novel analytical methods which either have not yet been used or have just been started to be used for characterisation of amorphous or co-amorphous pharmaceutical materials will be applied (i.e. solid-state NMR, molecular dynamics simulations). The understanding of fundamental thermodynamic properties, molecular interactions and reorganization processes in the co-amorphous systems will form the basis for the more systemic approach in designing and prediction of physicochemical features of the pharmaceutical co-amorphous materials.

The amorphous state itself and the theory of amorphicity are long-standing unsolved problems in the fields of the solid-state physics and material sciences. Thus, the scientific outcomes of this project i.e., understanding the grass-roots mechanism of formation, stabilization and dissolution behaviour of the co-amorphous systems at the macroscopic and molecular level may bring new light on amorphous state of APIs materials and amorphous state in general. We expect to gain a better understanding of stability mechanisms and pathways of devitrification or crystallization of co-amorphous materials governed by varied factors such as thermodynamic, kinetic and molecular interactions. The innovative approach of this project to application of a comprehensive thermal analysis may enable to promote these useful but rarely used techniques in the area of pharmaceutical technology sciences.