C.1. DESCRIPTION FOR THE GENERAL PUBLIC

The project aims to develop and characterise in detail the physicochemical properties of nanocrystals of cilostazol, a model poorly soluble drug used in the treatment of peripheral arterial disease. The objective of the planned research is to gain knowledge of the relationships between the conditions of nanocrystals generation process and their characteristics. The project will also answer the question to what extent the reduction of cilostazol particles size to nano scale can improve their solubility and dissolution rate in comparison to the material of larger particles.

Low water solubility, which characterises most of the drugs discovered today, is both a therapeutic and an economic problem. When the dose of such substances is administered orally (e.g. in the tablet form), it is not able to fully dissolve in the available quantity of gastric or intestinal fluid and its dissolution process is slow. As a result, only a fraction of the dosed amount reaches the circulation and the site of pharmacological action, which is referred to as low bioavailability. Moreover, the absorbed amount of the drug may depend on whether it is administered with or without a meal, which may cause variability in its blood level and negatively influence the safety and efficacy of pharmacotherapy. From an economic and environmental point of view on the other hand, low bioavailability of poorly soluble substances requires their considerably high usage in the manufacturing of tablets or capsules.

The search for ways of improving the solubility and dissolution rate of drugs is therefore an ongoing challenge for pharmaceutical technology. One of the solutions to this problem is the reduction of solid particles' size to nanometre range – the generation of nanocrystals. Liquid antisolvent precipitation (LASP) is among the methods which make it possible to obtain such fine powder. It consists of dissolving the drug in an organic liquid, in which it is soluble, and subsequently precipitating the crystals in a controlled manner by the addition of water, where its solubility is low. The application of ultrasound to the process (sonoprecipitation) allows to generate even smaller particles.

The solubility and dissolution rate depend on several solid particles parameters, such as size, shape and morphology or crystallographic form (polymorphism/amorphism). All these properties of the obtained nanocrystals are determined by the course of the precipitation process. Therefore, our project aims to study in detail these relationships. We will carry out a number of experiments where we will systematically observe the influence of different operating parameters values of LASP and sonoprecipitation on nanocrystals' size, other physical properties and dissolution rate. This way, we intend to study thoroughly the significance of such factors as the type and quantity of the solvent, type and concentration of stabilizer (substance used to prevent the agglomeration of precipitated particles in nanosuspension), drug concentration in solvent, mixing speed, or pattern and time of ultrasound application. As a result, an optimisation of LASP and sonoprecipitation processes will be performed, i.e. we will determine the values of aforementioned factors which result in the production of cilostazol crystals below 1 μm and dissolution rate higher than available raw material.

The precipitated nanocrystals will initially have the form of liquid nanosuspensions. To increase their stability and enable their further use e.g. for tableting, optimal samples will be dried by lyophilisation. Freezing and ice sublimation in this process generate stress which can cause nanocrystals agglomeration or polymorphic transformation. Because of this, the aim of this project is also a detailed study into the influence of different lyophilisation conditions and protective substances used (cryoprotectants) on nanocrystals' physical properties, which will be compared to size, dissolution rate and other features observed before drying. In addition, we will check how the temperature and humidity during storage of dried nanocrystals impact their properties (stability studies). A number of analytical techniques will be used in order to characterise the nanocrystals, including laser diffraction, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) or X-ray powder diffractometry (XRPD).

Owing to the proposed research, our project will contribute to the development of the scientific knowledge about solubility and dissolution rate enhancement technologies, and, in consequence, the bioavailability improvement of poorly soluble active substances.