Re-cocrystallization using supercritical carbon dioxide – novel green process for submicron cocrystal formation

Approximately 90% of new drug molecules undergoing clinical trials and 40% of currently marketed drugs belong to the Biopharmaceutical Classification System (BCS) II and IV classes, which suffer from poor water solubility and low bioavailability. As a result, the absorption of drugs in the gastrointestinal tract is limited, and their efficiency is hindered. One way of enhancing the bioavailability of drugs is their cocrystallization with a water-soluble coformer. Cocrystals are multicomponent crystalline structures comprising at least two pure components in a stoichiometric ratio (*e.g.*, a drug and coformer), interacting with each other via electrostatic interactions. By choosing an appropriate coformer, the bioavailability of poorly soluble bioactive substances can be improved. The U.S. FDA accepted cocrystals as new drugs in February 2018. Moreover, cocrystallization can also be used to reduce the evaporation/sublimation of volatile active substances, which is of interest for active food packaging development.

The crystallization to obtain the smallest possible crystals of active pharmaceutical ingredients with improved bioavailability is of the utmost importance for the pharmaceutical industry. Conventional crystallization and cocrystallization technologies employ organic solvents, and the lower limit for particle size is on the order of microns. In practice, the particle size is rarely obtained below 20 μm using conventional industrial crystallization techniques. To further reduce particle size, a micronization process such as jet milling is mandatory, which can result in degradation due to thermal and mechanical stress and loss in crystallinity. Supercritical carbon dioxide ($scCO_2$) is considered a green solvent, allowing for the design of environmentally friendly processes. There are a number of benefits of using $scCO_2$ in crystallization. These include a greener solvent choice, elimination of an additional drying step, elimination of a need to remove the residual organic solvent, and the ability to produce small particle size with narrow particle size distribution.

Within the project, a novel process for submicron cocrystal production using $scCO_2$ will be designed, and process parameters will be optimized for poorly water-soluble drugs (fenofibrate, carbamazepine, and dapsone) and bioactive substances of natural origin (usnic acid, esculetin, carvacrol, and thymol). Large cocrystals will be produced by a simple mechanical procedure without the usage of organic solvents. In the next step, the cocrystals will be dissolved in $scCO_2$ and subsequently re-cocrystallized during the decompression and cooling. With a proper selection of pressure, temperature, decompression, and cooling rates, submicron cocrystals will be produced in a free form or will be impregnated onto suitable carriers, such as foams of pharmaceutical and other biodegradable polymers and aerogels. As a result, obtained submicron cocrystals of selected poorly water-soluble drugs will allow for increased aqueous solubility of the drug. On the other hand, submicron cocrystals of highly volatile substances will allow for the controlled release of a volatile active substance (e.g., from food packaging). Experimental measurement of drug solubility in $scCO_2$ at different temperatures and pressures needed for the process design is time-consuming and costly. Therefore, the project will also contribute to solubility modeling using empirical and thermodynamical models. Molecular modeling will also be applied to understand the interactions between drugs, coformers, and polymers.

The outcomes of this project will not only provide crucial process parameters for high-pressure re-cocrystallization but also open up new directions in the pharmaceutical and food industries. The pharmaceutical sector will benefit from a solvent-free submicron cocrystal production process, enhancing the bioavailability of poorly soluble drugs. Similarly, the food industry R&D will gain a novel method of regulating the release of highly volatile active compounds from food packaging.