Assessment of twin screw extrusion potential as a continuous and scalable method of mechanochemical synthesis of active pharmaceutical ingredients

The production of drugs in agreement with the principles of 'Green Chemistry' has become a subject of interest of the pharmaceutical industry due to the high environmental impact of drug synthesis. In general, the negative environmental effects of 'traditional' approach are mainly associated with the excessive solvent use in the processes of synthesis and purification of active pharmaceutical ingredients (APIs), which causes safety and solvent recycling issues. Therefore, solvent-less or solvent-free methods of drugs synthesis might significantly decrease the environmental footprint of pharmaceutical industry.

Medicinal mechanochemistry is a term introduced to describe a new approach to drug synthesis which utilises absorption of mechanical energy to create new chemical bonds. It can be carried out under the solvent-free conditions allowing to reduce waste and improve safety of the conducted processes. Additionally, the shorter reaction times compared to solution-based synthetic routes and lower temperature settings during the procedures benefit energy efficiency of the manufacturing.

Currently, the main direction of the medical mechanochemistry development is exploring routes of synthesis leading to preparation of known molecules that have been, so far, synthesised exclusively *via* solvent-based methods. The most frequently employed technique to conduct those mechanochemical reactions is grinding in a ball mill. However, transfer of mechanochemical synthesis from a gram-scale batch-based grinding techniques to the industrial-scale setup, remains a challenge. Thus, a reactive twin screw extrusion (TSE) gains recognition due to its scalability potential and operating in a continuous manner, which makes this process easily transferable to the industry. Despite the wide use of extrusion process in various branches of the industry, the data on potential application of the reactive extrusion in a synthesis of drugs is limited, especially due to the lack of mechanistic knowledge and *in-situ* understanding of TSE process in pharmaceutical applications.

The proposed project aims at translating model APIs syntheses that have been already synthesised *via* grinding to a twin screw extruder and evaluating how adjusting the proposed parameters of TSE affects the quality of a synthesised drug. This knowledge is essential to optimise extrusion process in order to produce substances of pharmaceutical quality.

The planned research will include the synthesis of four model drugs in a ball mill and a twin-screw extruder, systematic optimisation of reactive extrusion processing parameters as well as characterisation of final and intermediate products (in-process and in-situ). The experimental work will result in the identification of the key parameters for the efficient continuous manufacturing of drugs of high purity and yield followed by the assessment of reducing the environmental footprint of the conducted syntheses. For this purpose, calculations of Green Chemistry metrics, e.g. *E*-factor, will be performed.

To broaden the possible application of new knowledge generated in this project and increase its impact on other branches of chemistry, model syntheses were selected based on various mechanisms of chemical reactions. In addition, the selected drugs are among the most commonly prescribed analgesic and hypotensive drugs in the world, of great clinical importance, whose industrial production exceeds 100,000 tons per year.

Importantly, the proposed project addresses a growing need for the development of sustainable large-scale production methods. In the pharmaceutical industry, understanding the critical parameters of the carried out processes is particularly important due to the possibility of impurities presence and the need to guarantee access of the patients to the high quality medicinal products. Additionally, this timely project addresses the issue of medicines shortages observed recently in EU. Europe needs a local system of drug manufacturing in a green manner, as the environmental footprint of traditional solvent-based approach is not acceptable. Thus, a twin screw extrusion process, being a solvent-less, scalable, green technique operating in a continuous flow setup makes a great candidate to be a novel synthetic reactor.