

Chirality plays an important role for the development of new drugs. More than half of the drugs currently manufactured consist of chiral ingredients. However, the individual enantiomers of a drug may differ with respect to biological activity, pharmacology, toxicology, pharmacokinetics, and metabolism. Usually, only one enantiomer interacts specifically with a cell receptor and provides a desired pharmacological outcome, whereas the other may have no effect, cause entirely different effects, or may even be harmful. Therefore, most of the new drugs marketed today are single enantiomers. The manufacturing of a chiral compound in an enantiopure form can be realized by stereoselective synthesis from a prochiral compound or derived from a chiral pool. Both these methods can provide products with high enantiomeric enrichment in a cost-effective way, however, they require an efficient catalyst, chiral auxiliary or precursor, applicable to bring about enantioselective reactions. Therefore, manufacturing of enantiomers under achiral conditions is usually more economical than stereoselective synthesis and is widely applicable. The products are formed as a racemic (equimolar) mixture of two enantiomers, which is subsequently subjected to downstream processing in chiral environment to isolate target enantiomer. There are various methods for the resolution of racemates such as crystallization, chromatography, special membrane technologies, with their strengths and pitfalls. The most versatile technique to perform enantioseparation is still chromatography. Currently, there is a growing arsenal of selective chiral stationary phases (CSP) available, which allow separation of a large spectrum of racemates at high separation selectivity, thus at high product purity that satisfies pharmaceutical requirements. However, chiral chromatography (CCh) to this moment is usually a cost driver of the whole production process, which stems from a high price of CSPs and their limited mechanical stability. In this project, we shall develop a more economical approach for the resolution of enantiomers that allows significant reduction in costs of the process realization. The approach is based on replacement or partial replacement of CCh with achiral chromatography (ACh) on plain silica gel, which is markedly cheaper for the realization. ACh shall be used to isolate the target enantiomer from mixtures enriched with the target enantiomer after asymmetric synthesis or after a preliminary CCh separation.

Despite identical physico-chemical properties of enantiomers, their achiral separation is possible in many cases. This stems from asymmetric interactions of certain enantiomers in the liquid and adsorbed phases due to the formation of homo and hetero-chiral associates with different adsorption properties. The occurrence of that phenomenon, termed as self-disproportionation of enantiomers (SDE), has been evidenced in literature for a number of different chiral compounds and claimed to be a reason of their chromatographic separation on silica gel columns. However, thermodynamics of such a process has not been quantitated yet. Moreover, the process dynamics of chromatographic separation involving SDE has not been described. Therefore, the goal of the project is to investigate and quantify asymmetric SDE interactions of enantiomers in liquid and adsorbed phases. For that purpose, a mechanistic model of such interactions shall be developed. This is a cognitive aspect of the project realization. Apart from that aspect, the description of the phenomena underlying SDE shall enable design and successful realization of separation of enantiomers exhibiting SDE on preparative and industrial scales.

Another goal of the project is developing a new approach for separation of SDE-phoric enantiomers by continuous chromatography, which is based on the so called simulated moving bed process (SMB). In the new concept proposed here, a cascade of two SMB units will be assembled, which consists of achiral and chiral fixed bed (ACh-CCh). Finally, the concept of the process shall be experimentally verified using a modification of semi-preparative SMB system in the cooperation with the research group at Max Planck Institute in Magdeburg.

In parallel, the effectiveness of separation of selected mixtures of SDE-phoric enantiomers by achiral crystallization (ACry) and its coupling with CCh (ACry-CCh) will be analyzed. In contrast to diastereoisomeric crystallization, no chiral environment i.e., no chiral resolution agent, is necessary for ACry separation, however a certain enrichment of the racemate with the target product must be created prior to the process realization, in similarity to ACh. The results will be compared to the performance of the coupling ACh-CCh in both batch and continuous operations. In the comparison, economic aspects shall be quantified: process productivity, yield, and the solvent consumption.