From one to multiple flows and back to ONE-FLOW

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Multiple flows Flow Chemistry provides chemical intensification. Novel Process Windows (NPW) achieve the latter through exploration of unusual and typically harsh process conditions with much enhanced activation and also chance for different selectivity pattern [Hessel, ChemSusChem 2013]. Several flow chemistries were developed via high-T, high-p, high-c (solvent-free; alternative solvent) concepts, leading to a boost of reactivity. This is complemented by the implementation of new smart electromagnetic activation modes (photo, ultrasound, plasma, microwave, etc. with their discrete rotational, vibrational, electron levels) as powerful alternative to temperature activation (Maxwell-Boltzmann theory: collision, momentum, probability). In these ways, NPW open new Windows of Opportunity for business. Once the single processing steps are intensified, they can be brought to a higher level of process integration and simplification. The micro-flow multi-step synthesis of rufinamide exemplifies how a complete continuous end-to-end pharmaceutical manufacturing can been realised in one continuous run. From such today's highly elaborated process machinery, the next step-change vision is to have smart synthesis equipment which operates biomimetic and largely autonomous: that 'March of the Machines' [Ley, Angew. Chem. Int. Ed. 2015] will, e.g., relegate process monitoring to central computer systems under the oversight of the 'Robo-Chemist' [Pedlow, Nature 2014].

ONE-FLOW The FET-Open project ONE-FLOW translates the 'vertical hierarchy' of chemical multistep synthesis with its complex machinery into self-organising 'horizontal hierarchy' of a compartmentalized flow reactor system – a biomimetic digital flow cascade machinery with just one reactor passage. To keep horizontal hierarchy manageable, orthogonality needs to be increased among the different consecutive reactions. The winning point of nature is to have invented catalytic cascades. ONE-FLOW will uplift that by enabling the best bio- and chemocatalysts working door by door. 4 synthetic flow reaction networks ('metabolic pathways') and 1 flow cascade driven by automated intelligence ('signaling pathway') will be developed, producing 4 Top-list 2020 drugs.

A functional solvents system serves as integrated reactor-separator for the 3-step flow cascade to (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol. The ethoxylated ionic liquid Among 110TM acts as phase separator for the biocatalyst alcohol dehydrogenase, increasing also its activity and stability. The system water/acetophenone/Ammoeng 110TM gives up to 5 metastable phases which turn with time to fewer phases. The large diversity of ILs (>10 exp 6) and conventional solvents (> 7000) opens up possibility for solvent modelling via the COSMO-RS method. We identified 2-hydrazinoethanol as best conventional solvent and also some IL candidates. Cost/LCA assessment and experimental screening will then guide to the final solvents of our "Multi-Step-Solvent-Factory".

We developed the first quantitative solvent selection methodology, to create a Functional Solvent Factory. A comprehensive assessment is done by applying a solubility model, followed by an economic, reactivity and safety assessment. SHE assessment is complemented by conducting an LCA (cradle-to-gate) to each solvent. From the solubility model, the amount of solvent needed is to be quantified, which combined with the LCA results will allow us to select the greenest solvent coupled with a quantitative impact assessment. This methodology is applied currently to conventional solvents, but can also and will be applied to ionic liquids, and develop.

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