Final publishable summary report (extract form project final report)

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Project title: Modern polymer-based catalysts and microflow conditions as key elements of innovations in fine chemical synthesis
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1 Final publishable summary report

1.1 Executive Summary

Grant Agreement number: CP-IP 246095-2 POLYCAT
Project acronym: POLYCAT
Project title: Modern polymer-based catalysts and microflow conditions as key elements of innovations in fine chemical synthesis

GOALS

The ambition of POLYCAT is to provide an integrated and holistic approach utilizing novel polymer based nanoparticulate catalysts and microflow conditions as key elements for innovation in fine chemical synthesis addressing especially pharmaceutical, crop protection and vitamin synthesis. Supplementary aspects are the use of “green” solvents, the development of scaleable (micro) reactor concepts and of a container based modular plant platform for the specific need e.g. of API synthesis. This requires discipline bridging efforts between chemistry, catalysis and engineering and will lead to the replacement of a number of reaction steps in chemical syntheses by catalytic ones using more active, selective and stable nanoparticulate catalysts. The project culminates in the demonstration of the approach by piloting at least two processes in industrial relevant scale.

MAIN RESULTS

Novel polymer based catalyst supports & Nanoparticulate catalysts
- Six polymer based supports: hyper-crosslinked polystyrene (HPS), microgel particles, ultrathin polymer layers on organic/inorganic core particles, dendrons and dendrimers, nano-structured macro-porous materials, and carbon nanotubes
- Iterative specific tailoring to the supports for nanoparticle deposition and process needs
- Demonstration scale synthesis of Pd@HPS catalyst and establishment of industrial scale protocol
- Demonstration scale synthesis of Pt/ZnO and NCNT catalyst

Catalysts immobilization in flow reactors
- Fixation of magnetic denron-based catalysts in flow microreactor with magnet array
- Covalent fixation of microgels and spherical polyelectrolyte brushes microchannel walls
- Immobilization of inorganic (Pt/ZnO) and organic catalysts (HPS) by washcoating on metal and ceramic foams, and stainless steel plates
- Inorganic (Pt/ZnO) and organic catalysts (HPS, NCNT) as fixed beds in flow reactors

Process development
- Batch and continuous processing of industry reactions (using cartridge type and wall coated reactors)
- Simulation tools applied for selected reactions catalyzed by novel catalysts
• Novel catalysts in use for the industry relevant reactions. Benchmarking running.

Reactor development and realization
• Microreactor performance evaluation and benchmarking; work on scale-up concepts
• Specific reactor development for demonstration reactions

Plant development and erection
• Detailed design adaptations of container plant concept (ECoTrainer) with regard to API synthesis
• Transfer of the mobile ECoTrainer and on-site installation

Demo plant operation
• Implementation of new reactors and catalyst systems into the basic chemical infrastructure of the ECoTrainer
• Successful operation for two industrial target reactions (hydrogenation and Suzuki cross coupling in context of API synthesis) validating POLYCAT catalysts and POLYCAT reactors

SOCIO-ECONOMIC IMPACT AND USE

Cost analysis & LCA
• Ex-ante cost analysis and Simplified Life Cycle Assessments are established as process development accompanying tool
• Full cost analysis and LCA for two demo processes (sugar hydrogenation, API intermediate) revealed potential for reduction of environmental impact and for cost decrease

Dissemination
• Broad range of publications and conference contributions; public website
• Special events: public dissemination event, student school, summer school.

Exploitation
• Patent applications on POLYCAT catalyst systems and their process application published
• Exploitable results in the area of reactor and plant technology, catalyst systems and catalyst coating technology

CONCLUSIONS

Novel polymer based nanoparticulate catalysts
Six novel polymer based catalyst system types applied for industrial reactions. Catalyst development supported by simulation. Corresponding immobilization technologies established.

Reactor and plant development & demo operation
Successful operation of new reactors and catalyst systems implemented in the ECoTrainer as novel plant concept for two industrial target reactions validating POLYCAT concepts

Cost & LCA analysis
Cost analysis and LCA done for demo processes

Dissemination & Exploitation
About 40 publications in peer-reviewed journals and 250 dissemination activities. Patent applications made and further exploitable results identified.

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1.2 Summary description of project context and objectives

1.2.1 Problem situation

Improving sustainability in all areas, e.g. science, business, society as well as policy, is the biggest challenge in our century. It was after the publication of the report “Our Common Future” by the Brundtland commission in 1987 when the idea of sustainable development started to spread over the whole world. Since this time, the content of this concept was defined more precisely in a wide range of agreements, action plans, national programmes, and scientific studies.

The chemical market in Europe faces large competition under considerable cost and ecological pressure, since new production capacities with lower cost structure are opened worldwide, raw materials become more costly, energy costs raise, customer demands on product quality increase, and society quests for reducing environmental footprint and industrial safety. Industrial production must respond to these changing needs in order to satisfy the increasing product requirements by the customer and the environmental, economic and social constraints of the industrial-scale process itself. The chemical industry as one of the biggest global players is exceptionally requested to discover innovative ways providing novel sustainable solutions of clean technologies reducing the pollution levels and the consumption of exhaustible resources. But, radical improvements can only be achieved by a complete rethinking of production processes which is meant by process intensification. This includes chemistry itself as well as new reactor configurations and novel process conditions (‘Novel Process Windows’).

Accordingly, prime issues and problems to be solved are here

- higher eco-efficiency via environmentally benign processes and atom-economical transformations
- higher resource efficiency by better selectivity to reduce waste and emissions
- novel synthetic reactions and process windows
- address specific transformations of functional groups
- use highly selective multifunctional catalysts and alternative solvents

Such step-changing goals are hardly achieved anymore by single improvements in the classical disciplines, but rather strongly demand for cooperation between branches of chemistry and engineering that have not traditionally worked closely together. Interdisciplinary routes are to be undertaken in order to notably improve the understanding of structure/property relationships at molecular level, to demonstrate breakthrough in synthesis and chemical transformation, to gain flexible and modular processing units with advanced process control for optimal production, ultimately inquiring compactness, system integration and miniaturization.

1.2.2 Main objectives

A key objective and strategic advantage with added value to society is to develop reactors, processes and plants for knowledge-based factories through holistic catalysis/chemistry and engineering concepts. These innovative production systems should target high added-value chemical products via new processing approaches covering and impacting the whole process chain. This demands for an integrated, coherent and holistic approach in the way as outlined below. Finally, such interdisciplinary efforts should have a clear industrial leadership evidenced by profound demonstration activities.
The **major goal** and breakthrough of the POLYCAT project and thus answer and ‘trouble shooting’ to the above mentioned problem situation is the **accomplishment of an integrated, coherent and holistic approach** utilizing novel heterogeneous polymer based nanoparticulate catalysts in vitamin, pharmaceutical and crop protection syntheses in conjunction with the enabling functions of microreactor technology and “green” solvents.

**INTEGRATED** – Innovation in chemistry by technology enabling functions

POLYCAT provides a discipline bridging approach between *fine chemistry, catalysis and engineering*. One very strong advantage at the **European level** is to combine the complementary expertise of chemists, chemical engineers and physicists from eight different institutions and companies all over the Europe.

We plan to develop general methodologies that would lead

- to the replacement of a number of chemical or micro-biological reaction steps in *fine chemical syntheses* by catalytic ones,
- to an increase of the yields of the existent catalytic steps by the replacement of conventional catalysts with more active, selective and stable nanoparticulate catalysts,
- to the development of novel chiral modifiers immobilized on heterogeneous polymeric supports, to a decrease of the amount of side-products,
- to a decrease of temperature and pressure of the catalytic reactions, and to the use of “green” solvents such as water, ethyl lactate or their mixtures with ethanol, ionic liquids or supercritical solvents.
- to new reactor concepts and processing routes.

**COHERENT** – streamlining demonstration with industrial relevance & high-impact

Rather than weakening the synergy of the efforts by diversifying into many, non-connected fields of applications, the demonstration activities of POLYCAT are focused on a few coherent and uniform class of chemistry and molecules and with targeted applications. In fine organic synthesis there is a wide spectrum of catalytic reactions. A few of these were selected with view on special impact for the catalysts in POLYCAT. The development of novel heterogeneous polymer-based nanoparticulate catalysts with permanent modification of the NPs by the functional groups of polymeric supports will allow the elimination of the disadvantages of traditional catalysts, the increase of the quality of the target product, the reduction in the production costs, and the development of a more environmentally sound production. The second selection criterion is the suitability and potential to flow chemistry, i.e. concerning the reactor and processing technologies of the partners with view on background know-how and IRP. Albeit the outlined focus, the selected types of catalytic reactions can be considered as representative for a later uptake of POLYCAT technologies to a broader range of chemical reactions.
As implementation and exploitation of the results is the final issue of POLYCAT, a holistic approach is followed which covers the whole process chain from screening over process development towards production. Always with view on a near-term utilization of results and to bring vision into reality, a real-case scale-up scenario for the use of micro process technology in pharmaceutical development is followed, as e.g. published by Lonza Company (Roberge et al., PharmChem, 2006, 6, 14). There is flexibility in each step to change between micro process and conventional technology aiming to explore more process steps for the first. At present, microstructured reactors are used primarily for laboratory development up to early piloting. The Lonza approach is hybrid in the time axis of process development.
1.3 Description of the main S&T results

1.3.1 Case study A: Carbon nanotubes & Nitrogen-doped carbon nanotubes for sugar hydrogenation

The hydrogenation of glucose to sorbitol (Fig. 1) was investigated within POLYCAT by various partners, including ThalesNano, TTU, BTS, AAU, TU/e and UNIJENA. Sorbitol is an important chemical produced industrially at 10^6 t/year scale a broad application e.g. in food and cosmetics industries. Conventional processes for sorbitol production typically employ batch type stirred tank reactors using Raney Nickel-type catalysts. There is, however, the desire to replace Raney Ni by non-leaching alternatives (e.g. Ru) and the classical batch processes by continuous technologies.

![Figure 1: Glucose hydrogenation to sorbitol.](image)

The performance of CNT and NCNT supported Ru/CNT and Ru/NCNT catalysts in continuous glucose hydrogenation was intensively investigated by AAU and BTS. Commercial Ru supported on activated carbon (Ru/C) was used as corresponding benchmark catalysts.

By initial screening a range of Ru/C and Ru/NCNT, Ru/CNT catalysts (prepared by different methods – see 1.3.4) in batch reactors, RuO_2/CNT, RuO_2/NCNT and the commercial Ru/C were identified as the most active and selective (pre-)catalysts (Fig. 2). Selectivity for sorbitol formation were typically found in the range 92-96%, Mannitol was identified as the most relevant side product.

![Figure 2: Catalyst screening in batch glucose hydrogenation: Conversion vs. reaction time multiplied by the amount of ruthenium in the reactor (Source: BTS, AAU).](image)

Interestingly, a size effect of Ru-nanoparticles on catalyst activity could be deduced from the experimental data: It was found that Ru-nanoparticles with a diameter of around 2.9 nm are the most active in glucose hydrogenation as compared to smaller or bigger particles (Fig. 3).

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Fig. 3 Dependence of initial glucose conversion rates on the particle size of ruthenium (Source: BTS, AAU).

The best performing catalysts, i.e. the RuO₂/NCNT and the commercial Ru/C benchmark, were then tested in continuous glucose hydrogenation using a parallel multiphase screening reactor setup as shown in Fig. 4.

![Parallel multiphase screening reactor setup](image)

Fig. 4 Parallel multiphase screening reactor setup (AAU) used for continuous hydrogenation of glucose to sorbitol (left). Comparison of NCNT and activated carbon supported Ru catalysts (right). Reaction conditions: T = 130°C, p(H₂) = 20 bar, c(glucose) = 0.2 mol/l, 2 mL/min flow rate. Glucose conversion (x): BTS-PC-L2: x = 91.4%, Ru/C: x = 41.5%. The selectivity towards sorbitol formation were found to be >98% for the two catalysts (Source: BTS, AAU).

Comparison of catalyst performance (as defined by the sorbitol productivity) of Ru/NCNT and Ru/C over a period of 3 hours indicated a gradual deactivation of the Ru/C catalyst, while the activity NCNT supported catalyst was stable. When the two catalysts (RuO₂/NCNT = Ru/NCNT = BTS-PC-L2 and Ru/C = Engelhard commercial sample) were subjected to a long term 100h testing run there was clear evidence about the superior properties of the NCNT supported catalyst as compared to the commercial sample: A strong deactivation of the commercial Ru/C catalyst over time on stream was observed, while deactivation of the Ru/NCNT catalyst was comparatively moderate (Fig. 5). It proved, furthermore, possible to regenerate the Ru/NCNT catalyst while the latter was not possible for the Ru/C sample.
**Fig. 5** Long term continuous glucose hydrogenation using commercial Ru/C catalyst and POLYCAT catalyst RuO₂/NCNT. Strong deactivation was observed for the commercial sample while deactivation was much less pronounced for the NCNT catalyst. Ru/NCNT catalyst was found to be reclaimable by thermal treatment with H₂ as indicated by increase in sorbitol productivity at t = 4500 min (Source: BTS, AAU).

Within POLYCAT TTU investigated HPS supported Ru/HPS (HPS = hyper-crosslinked polystyrene) catalysts in glucose hydrogenation, too. Excellent results regarding catalyst activity and selectivity were obtained for both batch and continuous glucose hydrogenation.

### 1.3.2 Case study B: Partial hydrogenations of industrially important precursor molecules

**Chemoselective hydrogenation of 2-methyl-3-butyn-2-ol with hyper-crosslinked polystyrene:** Selective hydrogenation of alkinols is one of the most widely studied industrially applicable catalytic processes. One of the approaches to the synthesis of long-chain unsaturated alcohols (i.e., isophytol) for the further production of tocols is a combination of C₃ and C₂ elongation reactions starting from acetone or citral.² The C₂ extension sequences are carried out by an ethynylation reaction followed by Lindlar-type and total hydrogenation.

![Synthesis of fat-soluble vitamins](image)

**Fig. 6** MBY as an intermediate in the synthesis of fragrant substances and fat-soluble vitamins.

One of the steps of isophytol synthesis is selective hydrogenation of 2-methyl-3-butyn-2-ol (MBY). The product of the MBY hydrogenation (2-methyl-3-buten-2-ol (MBE)) can be further used to produce linalool (Fig. 6), which can be regarded as a basic material for a large range of compounds (e.g.

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terpineol, geraniol and citral, and also used in the preparation of citronellol, ionones, Vitamin A, farnesol and sesquiterpenes). Palladium is well known to catalyze semihydrogenation of alkynes to alkenes. However, to achieve high selectivity along with high activity is still a challenge, which requires a careful choice of catalyst and reaction conditions.

In the framework of POLYCAT project, the TTU\(^3\) in collaboration with the EPFL\(^4\) have shown that the use of non-functionalized hyper-crosslinked polystyrene (HPS) as a support allows synthesizing the effective catalysts of MBY hydrogenation. The maximum observed selectivity in a batch mode was varied from 98.5% up to 99.6% at near total conversion depending on the reaction conditions and the Pd precursor nature. Along with non-functional HPS, the HPS material bearing amino-groups was also explored and MBE selectivity higher than 98% was found, that is remarkably higher in comparison with the data reported for common industrial Lindlar catalyst (Pd supported on Pb doped CaCO\(_3\)).\(^5\) It is noteworthy that all the synthesized HPS-based Pd-containing catalysts have low metal loading (varied from 0.2wt% up to 0.7wt%) along with high stability of catalytic properties, which makes them promising alternative for Lindlar catalyst (normally Lindlar catalyst contains about 5wt% of Pd).

For the Pd/HPS catalysts the influence of solvent nature, stirring rate, temperature and substrate-to-catalyst ratio was investigated. Besides, kinetic modeling was carried out and hypothesis on the reaction mechanism was put forward. Promising results were also obtained in continuous mode, however high pressure drop in the case of powdered HPS did not allow using such catalysts in microchannels.

At the same time, HPS bearing amino-groups was shown to be promising support for synthesis of Ru-containing hydrogenation catalysts.\(^6,7\) Thus, the CLARIANT, based on the Laboratory regulations provided by the TTU, has synthesized 3%-Ru/HPS catalyst (in granular form) in a pilot scale intended for selective hydrogenation of D-glucose for sorbitol production. Synthesized catalyst was found to provide selectivity higher than 98% at near total conversion of D-glucose and remarkably high stability (1000 h of work in a continuous mode using mini fixed-bed reactor).

**Chemoselective Hydrogenation of 2-butyne-1,4-diol to 2-butene-1,4-diol over Pd/PdZn/ZnO Catalyst:**

2-butyne-1,4-diol (B2D) is a compound widely used in fine chemistry and pharmaceutical industry as an intermediate. For example, B2D is a starting material for the syntheses of vitamins A and B\(_6\), pesticides, insecticides, etc. The conventional production of B2D involves a partial (triple to double bond) hydrogenation of 2-butyne-1,4-diol (B3D) which in turn is industrially produced from acetylene by its interaction with formaldehyde. A high selectivity of the B3D to B2D transformation is a crucial point of the whole process. A Lindlar catalyst (Pd supported on Pb doped CaCO\(_3\)) mostly used in this reaction can provide only a ~90% yield of the desired B2D. Moreover, this catalyst contains toxic lead.

During the POLYCAT project, the EPFL scientists proposed an effective method of controlling the reaction selectivity via placing Pd nanoparticles on a ZnO support. Upon heating in a hydrogen atmosphere a PdZn alloy is formed increasing the B2D selectivity up to 99.9%. For continuous applications, Pd nanoparticles were deposited on a ZnO layer coated on sintered metal fibers (SMF)

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and introduced within a micro-reactor. The developed structured catalytic reactor provided a considerably higher efficiency as compared to the conventional process.

1.3.3 Case study C: From catalyst to ECoTrainer implementation

In POLYCAT different types of catalyst material were synthesized based on either inorganic supports, e.g. zinc oxide, or polymeric matrices like hyper-crosslinked polystyrene (HPS), carbon nanotubes (CNT), magnetic dendron/dendrimer-based particles, soft microgels and spherical polyelectrolyte brushes. In a second step various noble metals were incorporated in such supporting materials for generating catalytic highly active nanoparticles, which were then tested for the different reactions of academic and industrial interest. With the decision of SARD to run a Suzuki cross coupling reaction (SARD7) in the demonstration phase the focus was set on the catalyst material of TTU (Pd/HPS) for coupling phenyl boronic acid with 4-bromoanisole (Fig. 7).

![Fig. 7 SARD's desired model reaction for the Suzuki cross coupling.](image)

With these conditions in hand IMM, EMB, ThalesNano and EvI designed in parallel the necessary reactors and flow charts for the lab plants and the modular container-based platform, called ECoTrainer, in which the demonstration of the desired POLYCAT reactions should take place.

After developing and testing the desired catalyst at TTU laboratories (see 1.3.4) CLARIANT prepared the necessary amount of material for the demonstration phase. The batch of homogeneously coloured granules contains 50 g of MN100 (amine-functionalized) HPS with 2 wt% Pd (Fig. 8). The granules have a diameter range of 0.5 - 1 mm.

![Fig. 8 Left: TTU's catalyst in granular form before; right: after applying in SARD7 reaction (Source: IMM).](image)

The batch of powdered HPS contains 144 g of MN100 (amine-functionalized) HPS with 2 wt% Pd (Fig. 9). The particles of the ground material have a mean diameter of 60 µm.

![Fig. 9 TTU’s catalyst in powder form: 2wt% Pd/MN100 (Source: IMM).](image)
Both types of TTU’s catalyst material were used as solid bulk filling material inside IMM’s tube-in-tube reactors (2 mL, 6 mL for powder catalyst, 50 mL for granular catalyst) and EMB’s cartridge reactor (6 mL, only granular catalyst). Details on the reactor development can be found in chapter 1.3.7. In order to prevent the leaching of support material each reactor was closed at every end with stainless steel frits (10 µm pores) and a PES membranes 0.45 µm pores).

After installation of the appropriate reactor types into the flow box of the ECoTrainer platform IMM performed experimental runs of the Suzuki cross coupling reaction between phenyl boronic acid and 4-bromoanisole using both the IMM plant and the EMB plant. One drawback was the high pressure drop generated by the fine particles of the powdered HPS catalyst. Here the fixed bed inside a 6 mL reactor tube resulted in a pressure drop of approx. 25 bar. This value did not allow the application of the IMM’s largest reactor module in combination with the powder catalyst. But by using the granular type of HPS’ catalyst no pressure drop was generated even in the largest reactor module of IMM. In general, all types of 2 wt% Pd/HPS showed an impressive selectivity of 80% with a conversion rate between 37% for small reactor volumes and 65% for the 50 mL tube-in-tube reactor within a run of 300 min. This data shows that the over-all goal of POLYCAT was achieved: a Suzuki cross coupling target reaction was performed with great success in continuous-flow plants installed inside the ECoTrainer applying TTU’s novel catalyst system, which has been developed in the course of POLYCAT.

1.3.4 Catalyst development

_CNT and NCNT based catalysts:_ Within POLYCAT both carbon nanotubes (CNT) and nitrogen-doped carbon nanotubes (NCNT) were investigated as catalyst support materials for application in several heterogeneously catalysed hydrogenation reactions of interest. The advantages of (N)CNT as catalyst support materials have been discussed in detail elsewhere. Their major advantages for flow applications targeted within POLYCAT include the (i) “open” mesoporous structure (ensuring proper mass transport properties in any (gas) / liquid / solid systems), (ii) a catalyst particle size 100 µm < d < 1000 µm favourable for continuous processing in fixed bed microreactors, (iii) a high mechanical stability as well as (iv) a high chemical stability due to strong metal-support interactions, which may also ensure reduced metal leaching from the heterogeneous M/(N)CNT catalyst. Tab. 1 gives an overview about (N)CNT supported catalysts investigated within POLYCAT.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction type</th>
<th>POLYCAT reaction</th>
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<tbody>
<tr>
<td>Ru/CNT</td>
<td>Hydrogenation</td>
<td>Glucose \rightarrow Sorbitol</td>
</tr>
<tr>
<td>Ru/NCNT</td>
<td>Hydrogenation</td>
<td>Glucose \rightarrow Sorbitol</td>
</tr>
<tr>
<td>Ni/NCNT</td>
<td>Hydrogenation</td>
<td>Nitrile hydrogenation, (R-CN \rightarrow R-CH2-NH2; Benzonitrile \rightarrow Benzylamine)</td>
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</table>

_Ru/NCNT and Ru/CNT catalysts:_ Ru/NCNT and Ru/CNT catalysts (Ru(N)CNT) were prepared by various methods as indicated in Tab. 2. The combination of catalyst syntheses by (i) colloidal, (ii) incipient wetness impregnation and (iii) precipitation deposition methods allowed controlling the ruthenium particles size over a wide range, i.e. 1.3 – 5.3 nm. Following route (i), Ru/(N)CNT were obtained on boiling a solution of Ru(acac)3 (acac= acetylacetonate) in ethylene glycol in the

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presence of polyvinylpyrrolidone (PVP) polymer. According to (ii) the (N)CNT support was impregnated with RuCl₃ metal precursor and PVP followed by (optionally) pre-calcination and reduction with H₂ gas at elevated temperatures. Route (iii) is based on the precipitation of RuO₂-nanoparticles onto (N)CNT support by addition of a H₂O₂-solution to an aqueous mixture of (N)CNT and RuCl₃. In various POLYCAT collaborations between BTS, TTU, ThalesNano and AAU the Ru/(N)CNT materials were tested as catalysts for glucose hydrogenation in batch and continuous mode of operation.

Tab. 2 Representative Ru/CNT and Ru/NCNT catalysts prepared for glucose hydrogenation within POLYCAT.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Method</th>
<th>Ru content;[1] NP size[2]</th>
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<tbody>
<tr>
<td>BTS-C, Ru/NCNT</td>
<td>Colloidal</td>
<td>4.1%; 1.5 nm</td>
</tr>
<tr>
<td>BTS-G, Ru/NCNT</td>
<td>Incipient wetness impregnation – calcination - reduction</td>
<td>3.4%; 5.3 nm</td>
</tr>
<tr>
<td>BTS-H, Ru/NCNT</td>
<td>Incipient wetness impregnation - reduction</td>
<td>3.6%; 3.3 nm</td>
</tr>
<tr>
<td>BTS-J, RuO₂/CNT</td>
<td>Precipitation deposition</td>
<td>3.3%; 1.3 nm</td>
</tr>
<tr>
<td>BTS-L₂*, RuO₂/NCNT</td>
<td>Precipitation deposition</td>
<td>2.2%; 1.4 nm</td>
</tr>
</tbody>
</table>

* BTS-L₂ was used for POLYCAT demonstration, i.e. long term continuous glucose hydrogenation. [1] ICP, [2] TEM

Fig. 10 shows typical TEM images of Ru/NCNT catalysts as obtained from colloidal synthesis (i) or via precipitation deposition (iii).

![Fig. 10 TEM images of Ru/NCNT catalysts prepared by colloidal method (BTS-C, left) and precipitation deposition (BTS-L2, right) (Source: BTS).](image)

In an alternative approach Ru/(N)CNT catalyst preparation by atomic layer deposition (ALD) was investigated at PICOSUN. The latter approach may bear the advantage of avoiding wet chemical surface activation steps and/or the need of surfactants. On the other side, rather expensive organometallic ruthenium precursors have to be used. Ruthenium was deposited on NCNT in the gas phase by ALD using [Cp₂Ru] metal precursor (Cp = cyclopentadienyl) and air. Before the depositions the NCNT sample was stabilized for 3 hours under nitrogen flow in vacuo, but any further pre-treatment steps were performed. Application of 50 ALD cycles on NCNT support at the deposition temperature of 350 °C led to the formation of the Ru/NCNT sample shown in Fig. 11. The Ru content as determined by ICP was found to be 1.6 wt%.
**Fig. 11** TEM image of Ru/NCNT catalyst prepared by ALD (Source: BTS).

**Ni/NCNT catalysts:** Ni/NCNT catalysts were investigated in nitrile hydrogenation as possible alternatives to Ra-Ni, which bears significant disadvantages for application in continuous processes. Ni/NCNT was prepared by (i) incipient wetness impregnation directly followed by reduction (Ni/NCNT\(^R\)) or (ii) incipient wetness impregnation – calcination – reduction (Ni/NCNT\(^C\)\(^R\)). Calcination of the Ni salt precursor (e.g. Ni(NO\(_3\))\(_2\)) before the reduction step (strategy (ii)) leads to the intermediate formation of well-defined NiO, which may bear advantages for the subsequent reduction step, e.g. regarding mono dispersion of the resulting metal nanoparticles.

**Fig. 12** Ni/NCNT catalysts prepared by incipient wetness impregnation–reduction (Ni/NCNT\(^R\); d(Ni) = 4.4 nm; left) and incipient wetness impregnation–calcination– reduction (Ni/NCNT\(^C\)\(^R\); d(Ni) = 6.2 nm; right). In both cases the Ni precursor used was Ni(NO\(_3\))\(_2\); (Source: BTS).

Ni/NCNT catalysts obtained from route (i) and (ii) were tested in batch hydrogenation of benzonitrile. They were found to be more active (per amount of contained metal) as compared to the benchmark R-Ni catalyst.

In summary, a variety of NCNT and CNT supported catalysts have been investigated including Ru/CNT, Ru/NCNT and Ni/NCNT. All these catalysts were tested in hydrogenation reactions in the laboratories of several POLYCAT partners. Partners involved in the area of (N)CNT based catalysts and their application were BTS (catalyst preparation and testing), PICOSUN (catalyst preparation via ALD), ThalesNano (catalyst testing in continuous glucose hydrogenation), Tver Technical University (catalyst testing in batch glucose hydrogenation), AAU (catalyst testing in batch and continuous glucose hydrogenation), University of Palermo (structure activity relationships via molecular modeling), UNIJENA (technoeconomic evaluation of glucose hydrogenation).
**Hyper-crosslinked polystyrene (HPS):** The TTU group developed novel polymer nanocatalysts based on hyper-crosslinked polystyrene (HPS). HPS is highly porous polymer consisting of rigid cavities, the size of which can be varied depending on the reaction conditions (Fig. 13).

![Image of a chemical reaction]

**Fig. 13** General scheme of HPS-based catalyst synthesis (Source: TTU).

HPS based catalysts allow control over NP formation due to a “cage” effect (by limiting the NP size with the pore size) along with controlling the precursors and reduction conditions. Besides, HPS has remarkable thermal stability. It was shown using TGA method that HPS is stable at a temperature up to 300 °C. Despite the temperature stability of HPS is lower in comparison with traditional supports such as carbon or inorganic oxides, the temperature of 300 °C is enough to provide reduction of metal-containing species impregnated in HPS matrix to form catalytically active phase. In the framework of POLYCAT project the TTU has developed Pt-, Pd-, Ru- and Au-containing HPS-based catalytic systems using various commercial HPS (produced by Purolite Ltd (U.K.) non-functional and the HPS material bearing amino-groups) in granular form as well as powdered one. Besides, the nature of the metal precursor compounds was varied to design catalysts containing NPs with high degree of mono dispersion.

Catalysts in granular form were shown to be promising in fixed-bed cartridge-type reactors operating continuous mode (e.g. in the reaction of D-glucose hydrogenation to sorbitol, at optimal reaction conditions the 3%-Ru/HPS catalyst revealed selectivity of 99.7% at 99.3% of conversion and high stability during the long-time testing (1000 h)), while powdered catalysts were found to be effective in slurry reactors in a batch mode (selectivity up to 99% were obtained in different reactions of fine organic synthesis such as oxidation and hydrogenation of mono- and disaccharides, hydrogenation of alkynols). Fig. 14 shows transmission electron microscopy (TEM) images of Pd-, Pt- and Ru-containing HPS-based catalysts and high resolution transmission electron microscopy (HRTEM) image of a single Ru-containing particle stabilized by HPS.

The general advantages of HPS-based catalytic systems developed by the TTU in POLYCAT project in comparison with existing industrial catalysts include: (i) large specific surface area (usually near 1000-1500 m²/g); (ii) possibility to work in virtually any solvent; (iii) high catalyst activity at lower metal loading due to formation of well-defined NPs vs. their aggregation in conventional catalysts; (iv) higher stability and lifetime due to the minimization of metal loss; (v) high selectivity without necessity to use catalytic poisons and metal-modifiers; (vi) prevention of NP aggregation during the reaction. The above advantages of HPS-based catalysts allow regeneration and multiple reuses of the catalysts developed and thus seem to be especially promising for exploitation in industry.

Dendron/dendrimer-based catalysts: The INEOS group developed a family of novel aromatic hyperbranched individual macromolecules called dendrimers and dendrons. The structure of dendrimers and dendrons was varied to determine its influence on the formation of magnetic NPs to be used in the development of magnetically recoverable catalysts. Figure 3 shows an example of such a dendron decorated with long hydrophobic tails on the periphery. The high thermal stability of the dendrimers and dendrons allows their use in the formation of iron oxide magnetic NPs via high-temperature organometallic routes leading to high quality magnetic NPs. The presence of dodecyl chains in the dendron periphery (Fig. 15 left) allows excellent stabilization of multicore iron oxide NPs providing magnetic recovery and additional stabilization of catalytic (Pd) NPs in the dendron shell (Fig. 15 right).
The Pd NP formation is finely regulated by both the molecular weight of the dendron and the amount of dodecyl chains on the dendron periphery.\(^\text{18}\) At the same time, it has also been shown that the molecular weight of the dendron influences the internal structure of iron oxide multicore NPs and as such, it provides a sensitive nanoscale control of the associated magnetic properties.

Furthermore, the catalytic activity was found to depend on the size of the Pd NPs that were immobilized on the magnetic NPs. These catalysts showed 98% selectivity and remarkable activity in selective hydrogenation of dimethylethynylcarbinol (2-methyl-3-butyn-2-ol) to dimethylvinylcarbinol (2-methyl-3-buten-2-ol) which is an intermediate product in syntheses of fragrant substances and vitamins E and K. Exceptional catalytic properties of these nanomaterials, as well as the easy catalyst recovery, successful repeated cycle-use and the catalyst stability make them promising for hydrogenation and great potential for a number of other catalytic reactions carried out with Pd catalysts.

HZB was active in the preparation and characterization of polymer-based nanoparticulate catalysts. Polymeric carrier particles with core-shell structures were applied for the immobilization of different metal nanocatalysts. As the core material, (crosslinked) polystyrene or inorganic silica were used. To access excellent stability in environmentally benign solvent / water mixtures, the shell was made of a positively or a negatively charged polyelectrolyte brushes. Depending on the experimental approach, the water soluble polymer can be attached by a grafting-from approach via photo-emulsion polymerization (polyelectrolyte brush).\(^\text{19}[10]\) Depending on the nature of the polyelectrolyte, different metal NPs can be immobilized. For example, Ni and Ru NPs were generated on the anionic poly(acrylic acid) brushes, Pd, Au and Pt NPs were synthesized on the cationic polyelectrolyte brushes (Fig. 16).

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\(^{19}\) M. Ballauff, Prog. Polym. Sci. 2007, 32, 1135.
were expensive and it may be a limitation groups. The produce idea is hydrogenation and with this ideal, the formation may be reduced by means of an interaction between polymer chains and metal NP. In principle, this makes the HZB catalysts promising candidates for a variety of industrial relevant reactions like the Suzuki coupling. The application of our catalysts within POLYCAT required an irreversible attachment to microchannel walls like stainless steel surfaces modified with Al2O3 or SiO2. By surface modification of the microchannel walls, the polymer-based nanoparticulate catalysts were covalently bonded.

During the POLYCAT project, an efficient heterogeneous catalyst for selective reduction (hydrogenation) of valuable multi-functionalized organic molecules has been developed by the EPFL partner. Noble metals (Pd, Pt) NPs are well known to be effective for hydrogenation of various functional groups. However, in the case of molecules containing several reducible functional groups it is often necessary to hydrogenate only one while keeping the other intact. This could save an expensive row compound. Unfortunately, pure noble metals do not provide such a high selectivity and rather promote the reduction of all groups.

The idea of the EPFL scientists was to improve selectivity of palladium NPs by creating a nano-alloy with electron rich metallic zinc. To do this, Pd NPs were first deposited on a ZnO powder and then heated in hydrogen. In this case, Pd NPs catalysed a partial reduction of ZnO leading to metallic Zn and PdZn alloy formation. The resulting Pd/PdZn/ZnO catalyst was tested in selective hydrogenation of alkynols – complex molecules containing both triple carbon-carbon bond and OH-groups. With the positive influence of Zn, the yield of the target product increased up to >99% meaning that expensive alkynol was completely converted to desired alkenol.

FORTH: Within the POLYCAT project, FORTH was involved in the development of novel heterogeneous microgel-based nanoparticulate catalysts. Functional polymer microgel particles were used as templates for the formation of catalytic active nanoparticles (NPs). The synthesis of the metallic NPs within the polymeric microgels involved first the interaction of the functional groups of the polymer with a metal precursor, followed by the reduction of the metal ions in situ to produce the metal or bimetallic NPs immobilized within the microgel particles (Fig. 17 left).

Fig. 16 Schematic structure of SPB-based catalyst (Source: HZB).

In the TEM image, the well dispersed metal NPs (Pd in this case) can be seen as darker spots, which are homogenously deposited on the spherical polyelectrolyte brush carrier particles. The benefit of the carrier architecture is attributed to the following advantages: i) there is almost no mass transfer limitation through an extended ultrathin (100 nm) polymeric shell since the diffusion time within the polymer network is in the range of milliseconds, and ii) leaching of the metal into solution may be reduced by means of an interaction between polymer chains and metal NP. In principle, this makes the HZB catalysts promising candidates for a variety of industrial relevant reactions like the Suzuki coupling. The application of our catalysts within POLYCAT required an irreversible attachment to microchannel walls like stainless steel surfaces modified with Al2O3 or SiO2. By surface modification of the microchannel walls, the polymer-based nanoparticulate catalysts were covalently bonded.

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FORTH developed a series of pH-responsive microgel particles for use as matrices for metal nanoparticle nucleation and growth. These microgels were based on polyacids, poly(methacrylic acid) (PMAA) or poly(acrylic acid) (PAA), and a polybase, poly((2-diethylamino)ethyl methacrylate) (PDEA), bearing carboxylic acid and amino functional groups, respectively. During the ‘POLYCAT’ project, FORTH prepared hybrid nanocatalysts based in five different metal NPs. More specifically, Au/PDEA and Pt/V/DEA nanocatalysts were prepared for use in the selective reduction of a nitro group of an Z/E-alkene isomer mixture to the amino group of the Z isomer, whereas Pd/DEA and Pd/P(M)AA nanocatalysts were synthesized for use in a Suzuki coupling reaction of 4-bromoanisole and phenyl boronic acid. Finally, a Ru/PDEA nanocatalyst was developed for use in the hydrogen borrowing reaction of 1-(2-aminophenyl)propan-2-ol. The preparation of Au/PDEA, Pd/PDEA, Pd/P(M)AA and Ru/PDEA took place in aqueous media under an aerobic atmosphere, whereas, the Pt/V/PDEA hybrid nanocatalysts were prepared under anaerobic conditions using dry tetrahydrofuran (THF) as the solvent.

The successful immobilization of metal NPs within the polymer microgel particles, their size and shape were studied by transmission electron microscopy (TEM) (Fig. 17 right). For all samples, TEM revealed the formation of spherical in shape metal nanoparticles with an average diameter ranging from 1.5 - 3.4 nm within the microgel particles.

1.3.5 In-silico catalyst development

In the following are summarized some case studies published, in cooperation with other POLYCAT partners, by the UNIPA researchers. Topics range from the design and implementation of the support and catalyst models to the elementary step and whole catalytic reaction analyses. Both structural and reactivity parameters, useful to the experimental partners, were picked out by the in silico approaches – some of which thoroughly original – which had been proposed.

Construction and characterization of models of hyper-crosslinked polystyrene: A simple algorithm involving classical molecular dynamics (MD) simulations was suggested to build up models of hyper-crosslinked polystyrene showing macroporous structure. The algorithm was composed by three consecutive stages: MD simulation of a single polystyrene coil, crosslink formation, and finally relaxation of the structure.
The models, which are differentiated by the crosslinker concentration in the initial polystyrene chain, can be characterized by employing tools of the small angle neutron scattering analysis and procedures associated to the crosslinking algorithm, which allows one to discriminate among the different kinds of crosslinks between phenyl rings and to calculate the crosslinking degree. A model of hyper-crosslinked polystyrene so characterized is useful to simulate the behaviour of a great number of systems of use in the applications of this macromolecule as substrate.

**Computational investigation of alkenols and alkyndiols hydrogenation on a Pd cluster:** The reaction path leading to the partial and total reduction of alkenols and alkyndiols with general formula R−CH2−C≡C−CH(OH)−R’ and R−CH(OH)−C≡C−CH(OH)−R’ (R, R’ = H, CH3) on a D3h symmetry Pd9 cluster where atomic hydrogen is available have been analysed by means of calculations based on density functional theory.

The results, analysed in atomistic details, suggest that small palladium clusters could be selective on the partial hydrogenation of triple bonds. The first energy barrier for the hydrogenation of the alkene derivatives is in fact much higher than the one corresponding to the hydrogenation of the triple bond. Further, the products of the partial hydrogenation, also when adsorbed on the Pd9 cluster, are largely more stable than the corresponding alkenol or alkyndiol parents.

**Structure sensitivity of 2-methyl-butyn-2-ol hydrogenation on Pd: computational and experimental modelling:** In the frame of DFT paradigms, the adsorption of 2-methyl-3-butyn-2-ol (MBY) and 2-methyl-3-buten-2-ol (MBE) on a Pd30 cluster, including both \{100\} and \{111\} faces, was studied along with the pathways involved in the hydrogenation, taking place on plane and low coordination (corner/edge) sites of given MBY/Pd30 and MBE/Pd30 surface configurations.

The calculated energetics, further validated by gas-phase and water-assisted gas-phase MBY and MBE hydrogenation, performed on well-defined size and shape-controlled Pd nanoparticles supported on SiO2, were able to explain the origin of the structure sensitivity and the high selectivity characterizing the title reaction when occurring in aqueous solution. The C≡C moiety of the MBY surface species indeed seemed to be mostly activated by plane sites instead of corner/edge atoms, whereas the MBE species appeared to have a different behaviour, with their C=C moieties typically being activated by low coordination sites.
DFT studies excluded that the overhydrogenation paths could be affected by the site topologies; hence, the role of plane, edge, or corner atoms should not be influential in setting the surface reaction mechanism, which as a consequence could be controlled by the adsorption energy, actually distinguished by different values on sites of different topology. The role of water in the selectivity to MBE, which characterizes the catalytic overhydrogenation of MBY on Pd nanoparticles, was also inferred.

**Density functional theory investigation on the nucleation and growth of small Pd clusters on a hyper-crosslinked polystyrene matrix:** Density functional theory calculations were employed to investigate the nucleation and growth of small palladium clusters, up to Pd$_9$, into a microcavity of the porous hyper-crosslinked polystyrene (HPS).

The geometries and the electronic structures of the palladium clusters inside the HPS cavity, following the one-by-one atom addition, are affected by a counterbalance between the Pd–phenyl (Pd–Φ) and Pd–Pd interactions. The analysis performed on energetics, cavity distortions, and cluster geometries indeed suggest that the cluster growth is dominated by the Pd–Φ interactions up to the formation of Pd$_4$ aggregates, whereas the metal–metal interactions actually rule the growth of the larger clusters. The elasticity of the hyper-crosslinked polystyrene matrix also plays an important role in the cluster development processes.

**N-Doped carbon networks: alternative materials tracing new routes for activation of molecular hydrogen:** The fragmentation of molecular hydrogen on N-doped carbon networks was investigated by using molecular (polyaromatic macrocycles) as well as truncated and periodic (carbon nanotubes) models.
The computational study was focused on the ergodicity analysis of the reaction and on the properties of the transition states involved when constellations of three or four pyridinic nitrogen atom defects are present in the carbon network. Calculations show that whenever N-defects are embedded in species characterized by large conjugated π systems, either in polyaromatic macrocycles or carbon nanotubes, the corresponding H₂ bond cleavage is largely exergonic. The fragmentation Gibbs free energy is affected by the final arrangement of the hydrogen atoms on the defect and by the extension of the π electron cloud, but it is not influenced by the curvature radius of the carbon nanotube systems.

1.3.6 Catalyst insertion into continuous-flow system

One goal of POLYCAT was the synthesis of different types of polymeric materials based on hyper-crosslinked polystyrene (HPS), carbon nanotubes (CNT), magnetic dendron/dendrimer-based particles, soft microgels and spherical polyelectrolyte brushes. Their polymeric architecture enables the synthesis of small nanometer-sized noble metal particles inside the matrix of the polymer. This combination enables the possibility to stabilize and handle such highly reactive nanoparticles for catalytic applications. One major focus is the immobilisation of such catalyst materials on surfaces of microchannels. This immobilisation allows the use of the catalysts under continuous-flow conditions in microreactors. In the course of POLYCAT different approaches were suggested and developed by IMM, CNRS, FORTH and HZB. Beside the “classical” immobilisation method using thermal treatment of dip-coated supports like foams or monoliths or reaction plates, also purely organic polymer-based catalysts were covalently attached on microchannel walls. One specialty was the reversible fixation of magnetic catalyst material in a capillary reactor via an array of 208 small magnets located in the housing of the reactor.

*Thermal treatment:* This route for catalyst fixation was used by IMM and CNRS for the inorganic catalyst material from EPFL. A suspension of powdered Pt/ZnO was used to dip coat various foams or monoliths prior to the thermal treatment at several hundred ° Celsius resulting in a continuous layer of catalyst material inside the porous material (Fig. 23). This method allows the use of powdered catalyst material without the well-known pressure drop generated by powder particles inside a fixed bed.
**Fig. 23** EPFL’s catalyst after use in a tube-in-tube reactor; stainless steel foam pellets before (left) and after washcoating with Pt/ZnO (right), and after incorporation into 50 mL tube-in-tube reactor (Source: IMM).

**Solid material filling:** As highlighted already in chapter 1.3.3 and 1.3.7 several catalyst materials were solely used as fixed bed in tube-in-tube or cartridge reactors. In case of powdered materials like Pt/ZnO or Pd/HPS the integration into flow systems was not easily achieved due to the high pressure drop generated by the fixed bed. In contrary any catalyst material having larger particles like granular Pd/HPS or (N)CNTs was incorporated into flow systems without any drawback regarding pressure drop. Due to this fact larger amounts of catalyst material were applied for both demonstration reactions using the 50 mL tube-in-tube reactor.

**Covalent fixation:** FORTH and HZB used this method to fix their soft polymer matrices onto flat surfaces and microchannel walls. As support and for easier analysis of the covalent fixation glass substrates and glass microreactors were used. After activation of the surface under oxidative conditions, a silanization was done yielding active surface groups. These functional groups were then used in a second step to bind the polymeric particles on the surface (Fig. 24). Intensive tests under flow conditions revealed the strong adhesion of the catalyst material on the surfaces.

**Fig. 24** Schematic representation of catalyst immobilisation used for functionalization of channel walls in a glass microreactor (Source: FORTH).

**Magnetic fixation:** The reversible fixation of catalyst material allows the change of catalyst without harsh mechanical or chemical stress or even without the disassembly of the reactor from the plant. With the catalyst material of INEOS in hand (see chapter 1.3.4), IMM designed a reactor concept which allows the magnetic fixation of the catalyst via an array of 208 small rare-earth metal magnets contained in the reactor’s housing. As one can see in Fig. 25 the magnetic particles are
aligned along the induction lines of the magnets yielding a reversibly functionalized surface for catalytic applications.

![Fig. 25 Reactor filling with catalyst suspension using two syringes and reversible fixation of catalyst material on one side of the glass reactor (Source: IMM).](image)

### 1.3.7 Reactor development

IMM, ThalesNano and EMB are using their expertise in microreactor technology for providing different types of reactors which are able to perform the demonstration reactions selected by SARD. In case of SARD2 reaction a gas-liquid-solid process had to be realized for the chemoselective hydrogenation of a nitro group close-by to a vinyl group. As catalyst material either platinum on zinc oxide powder or nitrogen-doped carbon nanotubes are used. Both catalyst types are applied to continuous flow synthesis as fixed beds inside tube-in-tube reactors (IMM) or cartridge reactors (ThalesNano). In case of Pt/ZnO also stainless steel pellets were coated with this catalyst material at IMM and used for filling one of IMM’s tube-in-tube reactor and EMB’s cartridge reactor.

IMM provided the concept of a mini fixed bed reactor. This reactor is based on a tube-in-tube design (Fig. 26 left). The inner tube has a volume of 2 mL for the catalyst bed. Both ends of the tube can be closed by stainless steel frits for keeping the catalyst contained inside the tube. It is surrounded by a second tube which allows thermal control of the inner tube. The tubes for feeding and withdrawing the thermal liquid were laser welded to the out tube. Three temperature sensors were implemented as well via laser welding into the inner tube for direct temperature measurement inside the catalyst bed. Standard Swagelok elements (nuts, ferrules and clamps) were used for connecting the reactor to any lab plant installations used at IMM during the demonstration phase of the project. The same concept was used as well for the medium-sized (6 mL) and large version (50 mL) of IMM’s reactor modules.

![Fig. 26 IMM’s mini fixed bed reactor concept used in POLYCAT (left, Source: IMM) and ThalesNano’s Phoenix reactor module (right, Source: ThalesNano).](image)

During POLYCAT ThalesNano finalized the development of a novel reactor module which is capable to perform chemical transformations at elevated temperatures up to 450 °C using heterogeneous...
or homogeneous catalyst material (Fig. 26 right). The Phoenix module can be controlled either as stand-alone product or in conjunction with a ThalesNano H-Cube Pro. The latter combination was used during the demonstration phase of the project in the EvoTrainer for the chemoselective hydrogenation in SARD2 reaction using Pt/ZnO as powder in a sealed cartridge.

For SARD7 reaction a single liquid phase process had to be established. The catalyst material for the Suzuki cross coupling is Pd/MN100 either as granules or as powder (see 1.3.3 and 1.3.4). In the first case the tube-in-tube reactors of IMM (see above) and the cartridge reactor of EMB were used during the demonstration phase. Contrary to the fixed bed concept for powdered and granular catalyst material SARD7 reaction was also performed with INEOS’ dendron-based material which was immobilized in IMM’s microreactor for magnetic fixation. This reactor concept is completely new and was developed for both visualization of the magnetic fixation process inside a glass microreactor and for performing SARD7 in a high pressure version with integrated heat exchanger.

In summary, the POLYCAT division of reactor manufacturers used their broad expertise to design and adapt reactor concepts to the challenging properties of the novel POLYCAT catalyst materials. These reactor concepts were then implemented inside the ECoTrainer for performing successfully the demonstration reactions as desired by SARD (Fig. 27).

![Fig. 27 Section-wise installation of plant equipment inside the Flow Box of the ECoTrainer (Source: IMM).](image)

### 1.3.8 Modular container ECoTrainer and its use in POLYCAT

*Chemistry in a small scale universal infrastructure allows small-scale production under real-life conditions:* The advantages of compact small-scale systems are obvious: compared with a commercial-scale multipurpose plant, the investment costs are relatively low and the market risk is significantly smaller. The experts can develop a process independent from the site where production takes place later on. This saves valuable time. Small scale chemistry produces substances with exact requirements for the market and customer. Moreover, it is no pilot plant in the traditional sense, as it serves later as a “real” production plant, often without extensive modification. Small-scale infrastructures enable fast and simple capacity adjustment: if the demand rises more than expected, production is expanded to several modules or can be directly transferred
to a large-scale multipurpose plant. This approach splits both investment costs and risks - not an insignificant factor for a company.

Above all, however, small-scale plants shorten the time from idea to market entry. Laboratory development and basic engineering - planning phases that are otherwise strictly separated - can take place simultaneously. This is possible due to the small scale infrastructure being not only the place where the new process is developed but where production is also planned. A reaction in the glass flask may work perfectly, but will it work in continuous production with pencil-thin reaction tubes as well? Air bubbles that have no effect on the stream in a thick pipe can cause big problems in thin ones. Will the pump that performed well for a few months in the laboratory suffice for continuous production lasting several years? Is the small heat exchanger from the laboratory constructed of a material with an adequate service life for real production?

Even the engineering is anything but trivial: space is limited and, therefore, valuable. Engineers must accommodate all the functionalities of a chemical plant in a space typically not much larger than a garage. Small is beautiful - but only if some central challenges can be overcome. On one side, small-scale production has specific technical requirements. Small volumes often lead to acceleration of the mass transfer. Thus, the measuring and control technology must be far more sensitive and faster than in large-scale plants. Acceleration of processes also need higher demands on the measuring technology. On the other hand, the short routes in the container enable far better heat integration.

**Small scale means a paradigm shift:** On the other hand, small-scale bridges the gap between laboratory, pilot plant, and real production. Because a small scale process is designed to be a continuous process, the engineer must work with structural elements, components, materials, and process parameters that also characterize the real-life production of the substance later on. For example, you need small pumps that run reliably and continuously for years, and materials with a long shelf life - things that are normally unachievable with standard laboratory equipment. To heat a reaction solution, a heat exchanger or coils have to be used from the beginning, not a Bunsen burner or water bath. When a substance mixture has to be separated through distillation, the process engineer uses a column in the small-scale process and not a rotary evaporator. For chemists, this is a true paradigm shift, since a pilot scale production process is usually discontinuous, while a commercial-scale process is often batch, sometimes continuous in pharmaceutical production. Another type of plant raises completely different questions: do I need the same logistics and division of labour in the small-scale process? To what extent can the chemistry of small-scale plants be automated? Because the space in the container is quite limited, multi functionality plays an important role: a pipeline, for example, can also function as a support or provide stability.

A complete plant in an extremely small space! How does that work in reality? Finding an answer to this question has been one of the objectives of Evl, SARD and Fraunhofer experts, in cooperation with other companies and several universities have been pursuing since 2009 in their work on the EU research project POLYCAT. As part of the project, Evl has partnered with SARD and the Fh ICT-I MM in Mainz (Germany) on the development of a fourth-generation room cell. The unique feature of the small scale plant will be its ability to be used anywhere. The supply system for water, process gases, electricity, heat, and data lines is designed in such a way that, theoretically, any chemical reaction can be run in it.
Fig. 28 The ECoTrainer mini-factory. Measuring only 3 by 12 meters, the container holds everything needed for production - reactors, process control technology, IT modules, storage space for feedstocks, elements for constructive fire protection, escape doors, and catch basins in compliance with the Water Management Law (sketch taken from Evonik Folio Magazin 2013 7/8).

A universal infrastructure standard is the key to success: The beauty of the idea lies in its versatility. For example, one can integrate a complete chemical plant, but also only one single reactor for a special downstream processing step. High-pressure technology, comprehensive safety technology, and an ultra-compact design are particularly important for the processes in the POLYCAT Project. The project also does demonstrate that the approach can be used to run reactions safely and easily under highly critical process conditions. The ECoTrainer of the fourth generation, an all-round room cell is available since beginning in 2013. The brand new ECoTrainer was transported to IMM nearby Mainz, where the synthesis parts for the active pharmaceutical ingredients (API) were integrated.

Modularization and standardization of the processual unit operation plays a key role in small-scale plants. A module comprises a particular plant area or component with certain technical requirements. As a rule, modules are (partly) standardized and prefabricated structural elements or component groups that accelerate the planning and construction of a plant and reduce the costs of operation. Small-scale design and modularization are mutually beneficial. A module may always be less than optimal because of the compromises one frequently makes between requirements, but it can be available fast and at a reasonable price. If the pharmaceutical, or more general, the chemical process is modular, the processes can be modified or swapped quickly. Inversely, modularization is advanced because function and design repeat themselves in small scale plants.

Prototypical for GMP and API Standard: the ECoTrainer: The work carried out within the framework of the POLYCAT project mentioned above builds on an existing prototype: the newest generation of small scale production - the ECoTrainer. With the ECoTrainer, developers have already placed an important issue for nearly all pharmaceutical processes front and center: the means of supplying raw materials, energy, water, and data lines. Such infrastructure is needed for chemical / pharmaceutical processes to run at all, but at the same time, they account for as much as half of the investment costs of a conventional plant.

Several expansions of the ECoTrainer have been realized over the past years. Time and new components have been integrated, improved, and implemented for different pharma processes. This can be successful only in cooperation with the user. Thanks to the integrated planning process
and close cooperation with the production and research colleagues of SARD and IMM, it took less than three years to conclude development, all the way through to continuous production. In this period, engineers were able not only to optimize the process and design the required equipment, but also to prepare the ECoTrainer for API production in Mainz (Germany), commission it, and transport it to the final production site of SARD in Paris. The team of experts from Evl see themselves not only as service providers. With its innovative, small-scale ECoTrainer GMP/API option, the team supplies the basis for significantly reducing the time from product idea to final production process.

**On-site processing at IMM:** The main goal of POLYCAT is the application of novel polymer-based catalyst material immobilized in microstructured reactors and plant equipment for the synthesis of fine chemicals in conjunction with the integration in the modular container-based platform ECoTrainer for demonstration (Fig. 29). The academic partners of the POLYCAT consortium developed several concepts for the synthesis and analysis of novel polymer-based catalyst materials and realized their application in hydrogenation and oxidations reactions, and for Suzuki cross coupling. With these materials in hand it was the task of the reactor designers to provide appropriate equipment which allows in conjunction with the new catalysts their use in continuous-flow synthesis. Both hydrogenation and Suzuki cross coupling are perfectly suited for the use in microstructured equipment due to the excellent heat management, gas-liquid contacting and the possibility to test the novel POLYCAT catalysts on leaching during the Suzuki cross coupling reactions. These boundary conditions, novel polymer-based catalysts for SARD2 and SARD7 reactions for continuous-flow synthesis in microreactors, are the starting point for the development of the flow charts as base for the demo plant and its integration into the container-based platform ECoTrainer. Efficient interaction and collaboration between SARD, Evl, EMB, ThalesNano and IMM resulted in a highly integrated, fully functional demo plant inside a mobile container for the continuous-flow synthesis of fine chemicals.

![Fig. 29 The mobile ECoTrainer 4G: Infrastructure for product development from lab to production (Source: IMM).](image)

1.3.9 Ex-ante Cost Analysis to monitor Economic Viability + foster Process-Options Decision

**Evaluate ex-ante to minimize risk and maximize success:** Process intensification means a step change both in process equipment and processing. Accordingly, gain is high, yet also the risk.

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of the risk is non-technical, related to uncertainty about the environmental impact and, the cost competitiveness. To minimize such risk, it is advised to use cost analysis (and life-cycle assessment) as guidance before the experiments (‘ex-ante’); finally both in a multi-criteria manner. In such way, the best-prepared-for-success process option can be selected out of an almost infinite, confusing large choice of scenarios. This serves then to (i) act as an controlling and internal evaluation body with respect to industrial effects and environmental impacts, ii) give directions for technology choice prior to developments by rough calculations, and iii) accompany and support the on-going progress of green process design by means of quantification of the resulting environmental impacts.

**POLYCAT application showcases examined:** The task of TUE within the POLYCAT project was to present a methodology for ex-ante analysis to quantify overall process costs as well as main cost contributors and discuss economic viability of the diverse process/catalyst options. This included the processes under development in POLYCAT as well as superficial processes with learning potential for POLYCAT. The investigations were split in a three-fold manner as follows, to showcase first the two major innovation driver, i.e. the micro-flow processing and the POLYCAT catalysts, and thereafter their combined effect for an industrial chemical production process:

1. **Cost analysis of potential microreactor-based process** for the glucose oxidation and comparing it to the conventional process = using noble metal and enzyme catalysts for bulk chemical process where raw materials are cheap and widely available.
2. **Cost analysis of the innovative POLYCAT catalyst preparations** with the focus on the HPS based catalysts.
3. **Cost potential analysis of combined effects 1. + 2. at real-case industrial process** for process optimization + intensification for API synthesis performed on industrial scale at SARD Company.

**Results for microreactor use at glucose oxidation:** A complete analysis of the conventional batch glucose oxidation process and a hypothetical continuous microreactor-based process was presented. A falling film microreactor (FFMR) was chosen as an intensified reactor option, since it can handle gas-liquid-solid systems without much operational difficulties (e.g. pressure drop, replacement of coating) and is a reactor design familiar to chemical industry. It was calculated that glucose oxidation reaction performed in a numbered up FFMR would have lower final costs than current batch process, mainly due to the much reduced operating costs (Fig. 30 left).

![Production costs for 3 process options](image)

*Fig. 30* Production costs for 3 process options (right); respective operational costs split into portions (Source: TU/e).

Moreover and generically more relevant to the POLYCAT project, several detailed insights in the cost contributions adding the OPEX and CAPEX were determined. From Fig. 30 right it is evident that the catalyst is a key cost contribution to the overall process costs and that justifies respective POLYCAT efforts. It was in particular found (not shown in the figures) that, in case of using enzymes as ‘green
catalysts’, the costs for their immobilization contributed significantly and actually varied notably between the different enzymes under consideration. Thus, optimizing this process (rather than optimizing, for example, microfabrication) is a key in cost efficiency. However, very different numbers of runs needed for efficient commercial use were determined; some considerably above commonly agreed thresholds for use in bioprocess technology, showing the major hurdle in implementation of enzymatic processes.

**Results for innovative POLYCAT catalysts:** A cost analysis included catalyst preparation cost and catalyst process cost (see Fig. 31). It turned out that HPS based Ru and Pd catalysts are economical for glucose oxidation (as being of interest for the partner BTS) and DMEC hydrogenation reactions (as tested by the partner TTU). This statement is naturally valid for the assumptions documented so that these are to be considered the relevant outcome of the study and shall serve as development foci? Among these and very relevant from a practical point of view, is the rate of deactivation, which has been set to 0.01 and 0.1 h⁻¹. Even with such tribute to real-life, the above statement is valid. The projected costs of Pd/HTs range between 10 – 60 Euro/g which is in the range provided by commercial crosslinked polymer catalysts (for example by Sigma-Aldrich and Alfa Aesar). Further detailed insight on cost details and economically requested number of runs are given in the table below:

![Table](image)

**Fig. 31** Product and catalyst costs for three processes, finally determining numbers of runs needed (Source: TU/e).

**Results for combined effect on industrial reaction:** A methodology was developed for a techno-economic evaluation concerning optimization and intensification of an established pharmaceutical production of an anti-cancer drug at SARD plant site in Vitry-sur-Seine. Reaction step is a stereo- and chemoselective reduction of aromatic nitro groups in the presence of alkene functionalities to the respective Z- and E- amino compounds. The Z-isomeric compound is the economically valuable one.

With the scale of 100 kg/y and a product value of a few thousands Euros per kilogram, also following a general trend in pharmaceutical industry, this process is an ideal candidate for continuous, modular plant production of a highly potent drug and stands for the whole class of similar compounds. The impact of various chemical process parameters on the overall production costs has been investigated and process performance represented in terms of operation time, waste and resource usage as the main process metrics. Six optimized and intensified scenarios were compared to the reference case operated at SARD site: intensified reaction, continuous processing, change of solvent, change in the purification sequence, recovery of the key product and intensified drying option. The analysis has shown that, under the assumptions used, an intensified millireactor based process with a subsequent continuous post-processing brings the most benefits both in
terms of cost and performance. The total product cost has been reduced for 37 %, while the operating time was 27 % lower than the base case, with 26 % less waste and 46 % less labour needed.

The fraction of cost reduction per category for all six scenarios compared to the reference case is given in Figure 3, indicating the largest overall cost reduction potential for continuous reaction and continuous processing. An additional advantage can be gained by increasing the overall process yield (KOM recovery scenario) although it faces a higher capital investment. A cash analysis was further done and compared three selected scenarios (Fig. 32) to the reference case. All these scenarios give higher net present values. The net present value is up to 45 % higher for continuous processing than for the reference case.

![Table showing cost reduction](image)

**Fig. 32** Product and catalyst costs for three processes, finally determining numbers of runs needed (Source: TU/e).

In a more far-fetched and generic sense, the SARD process cost study has shown that process intensification is more powerful than process optimization and that there is considerable cost saving potential by flow separation (in the same order as for flow reaction); likely for other API hydrogenation reactions and reactions of similar separation footprint and process conditions as well. Future investigations will broaden the view, but this POLYCAT work has set the first brick. It is finally interesting to note that the life-cycle assessment gives a differentiated, partly contradictory picture, since the solvent dilution, which is currently unavoidable in case of using flow, affects negatively several of the LCA categories.

**Weight cost and environmental evaluation = eco-efficiency:** As final result, the cost analysis was coupled to life cycle impact assessment to define the overall eco-efficiency of the different process options for the SARD process. This is given in the UNIJENA report and shows that POLYCAT truly reached his holistic mission in the process evaluation (which is completed by comprehensive patent and process analysis, see papers given below). In this way, the eco-efficiency portfolio reveals the high environmental as well as economic benefits by transfer of batch to continuous combined with using innovative heterogeneous catalyst fixed in a tubular reactor. Such conclusion is given when the relative weights of cost and environment are the same and even when being different it will remain. Thus, even complexity in judgment will have no major impact in giving straightforward answers with certainty in there meaning.

### 1.3.10 Decision Support towards Sustainable Processes

In order to ensure the development of sustainable process alternatives, comparative environmental and cost analyses as well as holistic decision making procedures were followed within POLYCAT by the partner Friedrich Schiller University Jena. Herewith, focus was given for life cycle approaches covering all life cycle stages of a process or product system and combined with an iterative screening and optimization procedure. If the implementation of process design, optimization or
intensification concepts is accompanied by such assessment tools, the chances of developing more environmentally benign and economically competitive processes can be enhanced significantly.

The POLYCAT sustainability approach can be explained at best by means of a successful case study dealing with the re-design of an existing pharmaceutical production process,\textsuperscript{23,24} already introduced as one example for ex-ante cost analyses. Although pharmaceuticals are usually produced batch-wise yielding only a few tons annually, environmental aspects and production costs are significant. This is due to the long-chain production pathways and high efforts for active pharmaceutical ingredient (API) isolation and refining. Here, process intensification, coupled with flow processing is seen as important tool for optimization of existing procedures, offering, e.g., shorter and more efficient process development or scale-up activities, safer and more efficient production resulting in lower waste and environmental impact generation as well as less production costs.

The process discussed in the following results in the production of an anti-cancer drug at SARD plant site in Vitry-sur-Seine, France. The study was performed in parallel to experimental investigations to point out most relevant weak points of the current process and to show promising pathways to improve its overall environmental balance and cost competitiveness to be directly implemented in the ongoing re-design activities. The API production is based on a stereo- and chemoselective reduction of aromatic nitro groups in the presence of alkenes. The production scale is 100 kg/year, indicating a low volume, high value API. The main bottlenecks of the process were a low reaction efficiency, a high solvent consumption, fresh catalyst used for each batch, high material losses along the process chain (mainly due to purification and crystallization steps) and, as a result, a high waste production rate. Resulting from an initial process analysis performed by Eindhoven University of Technology, different strategies of optimization became clear: the change of the catalyst towards a heterogeneously fixed novel nanoparticulate catalyst, continuous operation mode using intensified millireactors, optimization of the product isolation and recovery as well as development of strategies reducing solvents and/or replacing hazardous solvents. By performing profound cost and LCA analyses, bottlenecks or process improvement potentials connected with these measures could be investigated in detail and recommendations for further process development could be given directly during development process (see Fig. 33).

\textbf{Fig. 33} Example for detailed LCA investigation of different process design alternatives with (AP) existing process and (BP 1 – BP 6) different batch alternatives.\textsuperscript{23}

In order to get the whole picture, the effects of single and coupled process parameter variations, considering, e.g. the change of reduction agent, change of crystallization approach, change of

drying procedure were taken into account as well. In accordance to the PI approach followed within POLYCAT, the next step evaluated was the transition from batch to continuous processing using a heterogeneously fixed, more effective catalyst in a ThalesNano H-Cube® system. By means of this, solvent demand for catalyst separation and product stream purification can be reduced.

Thus, process optimization options already evaluated for batch processing were coupled with the benefits of continuously running, heterogeneously catalyzed processes. Since yield enhancement was identified as one main key criterion, more effective downstream processing was found to have a significant impact on the resulting environmental balance under these conditions. If recovering KOM from waste stream, yield enhancement would result, e.g., in a reduction of the Global Warming Potential (GWP) and Human Toxicity Potential (HTP).

Within future developments, the environmental benefits and cost savings could be maximized by multi-parameter changes (e.g., continuous, heterogeneously catalysed processing coupled with direct crystallization and improved downstream-processing) as demonstrated for CP 5a in Fig. 34. The environmental burdens resulting from the preparation of heterogeneous catalyst were found not affecting the overall environmental balance in a great extent anymore (as it does in case of the existing slurry batch process), provided that the catalyst consumption is reduced by fixation and the catalyst activity remain stable over time. These requirements could be met by the project partner EPFL.

![Image](image.png)

**Fig. 34**  Example for eco-efficiency outranking of production alternatives with (AP) existing process, (BP 1 – BP 6) batch conditions and (CP 1 – CP 6) flow conditions according their environmental and cost efficiency; Parameters: criteria weights: equal, linear minimization of LCIA criteria and costs.24

Concluding, by transition from the conventional API manufacturing process to the best case within above discussed concepts, CP 5a, impressive saving potentials of, e.g., 765 kg CO₂ equivalents (GWP) and 65 kg Fe equivalents (Metal Depletion Potential) per kg API can be expected. Also significant total production cost savings up to 33 % can be gained, when the concepts developed within POLYCAT are implemented in industrial practice.

### 1.3.11 Industrial perspective

The pharmaceutical industry in Europe is currently facing stiff competition and considerable cost and ecological pressures. This is due to several factors: new production capacities with lower cost structure are opening worldwide, raw materials are becoming more costly, energy costs are rising, customer demands on quality increase, and society quests for reducing environmental footprint.

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and industrial safety. In particular, development and production of active pharmaceutical ingredients (API) must respond to these changing needs in order to satisfy the increasing requirements by the customer and the economic and environmental constraints of the API manufacturing process itself.

In the past, the decision making in API process development was mainly driven by cost factors. Currently, it is driven also more and more by increasing demand for green chemistry and engineering concepts. In order to develop economical and efficient environmentally benign processes, a “rethinking” of API manufacturing that integrates the chemistry with new equipment configurations (compactness, miniaturization, versatile, micro-structuration) and with process conditions (continuous - new process window) seems to offer advantages. This “rethinking” should be done as early as possible in the process development pathway as it is not often practical to redesign and optimize already established processes later on! An integrated and coherent approach – including cooperation between branches of chemistry and engineering, cost analyses (CA), and a holistic life cycle (LCA) – will pave pathways towards competitiveness and sustainability.

The standard development scheme from therapeutic concept to highly active pharmaceutical ingredient (HAP) for oncological therapeutic domain is summarized in Fig. 35.

**Fig. 35** Standard development scheme from therapeutic concept to highly active pharmaceutical ingredient including the associated need of HAP.

SARD Vitry is focused on research and process development, from chemical support to Discovery, to development of API manufacturing processes, to supplying batches for the overall development program (preclinical and clinical activities), and finally to transfer to industrial production units.

**Fig. 36** Focus of SARD Vitry on research and development.

Although HAPs are usually produced by batch processes, with volumes of less than a few hundred of kilograms annually, the potential environmental issues are indeed significant. Even though batch technologies (lab, pilot and plant) serve well the current development model, a potential improvement would be to highlight and manage environmental aspects of the process during the development phase of a project. Process intensification at the reaction process level\(^{25}\) should lead to economic and environmental benefits by improving safety, toxicity, cleanability and by enhancing quality by design (QbD).

For SARD Vitry, a prime focus has been to reduce catalyst handling and to reduce contamination of products by residual metals, aspects which are often associated with the use of homogeneous

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\(^{25}\) Selective catalysts and miniaturized reactors and continuous flow processing are considered prime enabling technologies for overcoming drawbacks in conventional batch production and achieving chemical process intensification.
catalysis. A second focus has been to reuse catalysts during a manufacturing campaign. With this objective, SARD Vitry has examined selective transformations of chemical functional groups via supported or grafted solid-phase catalysts with or without hydrogen gas.

The POLYCAT program provides an integrated, coherent (between fine chemistry, catalysis and engineering) and holistic approach to using novel polymer-based nanoparticulate catalysts in conjunction with the enabling functions of micro process technology. As this approach is in line with SARD’s own goals, SARD decided to participate in the program. In particular, SARD’s contribution has been to evaluate typical chemical reactions such as the Suzuki coupling of a bi-chlorinated pyridazine with phenyl boronic acids (SARD7 model) and the selective hydrogenation of a nitro group in presence of an alkene (SARD2 model). Noble metal-based chemical catalysts, and polymer supported smart structures have been explored, housed in a fixed bed, falling film microreactor or magnetic microreactor. A multi-purpose, modular container-type pilot infrastructure, ECoTrainer®, integrates individual modules in a block format, and standardizes basic logistics, process control and safety installations. The replacement of batch chemical reaction steps by catalytic continuous ones using active, selective and stable nanoparticulate catalysts has been successfully demonstrated and ultimately extrapolated in the ECoTrainer® to demonstrate the industrial applicability to the pilot scale. As an illustration, for SARD2, environmental efficiency significantly increased while a total cost reduction of roughly 25 % is predicted due to the reductions in processing time, capital costs as well as operational costs.

As conclusion, transforming the innovative solid catalyst into an intensified continuous process with an innovative reactor design at an early stage of development offers significant short- and medium-term advantages. Especially, it should allow SARD Vitry teams to avoid redesigning chemistries from candidate selection to first batches for toxicological studies, or to first administration in human. Two reactions of current early-development HAPs could benefit from microstructures POLYCAT: the chemoselective hydrogenation of a nitro group in presence of an acrylamide function, and the regioselective hydrogenation of a nitro group in presence of a second nitro group. In addition it would facilitate later transfer of solid catalysed reactions in pilot plants or in production plants (extrapolation and technical transfer); a hybrid-in-multistep implementation of ECoTrainer® microreactors integrated in the full manufacturing chain in SARD Vitry could reduce timelines through its intrinsic functionalities and by facilitating the use of hydrogen gas, and it could be co-operated with batch equipment up to 1 to 2 kg/day (2 shifts). The development of complementary units such as a continuous crystallization unit, or a filtration and drying unit are still in the “conceptual stage”. While the realization of a full continuous container pilot plant still remains a middle- to long-term challenge, the key reaction step can certainly be intensified by using continuous miniaturized reactors, which is now an established and available technology. POLYCAT ECoTrainer® is to be an enabling concept for the “process development unit of the future”.

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26 Multi-purpose continuous “catalyzed reaction unit” housed in a mobile HAP container with disposable microreactors
27 Pilot scale criteria or drivers: (1) rapidly configurable continuous skids for modularization, standardization, cleanability and intrinsic safety (2) could be co-operated with batch equipment up to 1 -2 kg/day (8 h-16h/day based) (3) versatile catalysts’ anchoring approaches enabling an easy use of microreactors such as magnetic field, disposable surfaces coated, fix bed - matrix based catalysts (4) avoiding homogeneous catalysis disadvantages: catalyst filtration, difficult recycling and metal contamination (5) minimal extrapolation: roughly same scale for development and first batches manufacturing and a modular architecture to faster technology transfers (6) small footprint facilities: capital cost reduced.
1.4 Potential impact, main dissemination activities and exploitation of results

1.4.1 Potential impact

Introduction

The POLYCAT project proposal was a response to the call for projects “NMP-2009-3.2-1 Innovative pathways for sustainable chemical production” within the EU FP7 Programme 2009, Cooperation, Theme 4 – Nanosciences, nanotechnologies, materials and new production technologies (NMP). This call was part of the subactivity “Adaptive production systems” in the activity “New production”. The programme text is setting the scene also with regard to expected project impact. Under “New production” it is stated that “A new approach to manufacturing is required for the transformation of EU industry from a resource intensive to a sustainable knowledge-based, eco-innovative industrial environment ….” This is developed further for the subactivity as follows: “The key objective is to develop production systems and elements for knowledge-based factories through holistic manufacturing engineering concepts. The systems should automatically and continuously adapt production resources and processes in an optimal way with respect to business and production objectives as well as market and technical conditions. ... The scope includes discrete manufacturing and process industries, supporting also the trend towards miniaturisation, as well as construction.” In the specific topic (NMP-2009-3.2-1) the technical scope/content is outlined as “Within the multi-annual strategy for promoting sustainable chemistry, the aim is to achieve more eco-efficient chemical syntheses and corresponding processes with high resource efficiency and reduced amounts of waste and emissions. This complies with the continuous transformation of energy and capital intensives sectors developing safe environmentally friendly reactions, products, and processes that will improve competitiveness within the chemical industry.” Furthermore, the following expected project impact is specified: “Expected results should provide a strategic advantage and added value to society, in terms of competitiveness, reduction of environmental footprint and industrial safety. Projects should contribute to the renewal of scientific and technological breakthrough in synthesis. 25-30% improvement in resource efficiency and yield is expected combined with a global target of zero-waste production for at least 20% of existing reactions.”

(Potential) Impacts of project and of its achievements

The European chemical market is under considerable cost and ecological pressure, especially in view of the new emerging markets and production capabilities in Asia. The project results of POLYCAT will contribute to an increased competitiveness of chemical and pharmaceutical industry and sustainability of chemical processes as should be tangible by the description of the main S&T results in Chapter 1.3. To underline this further, an insight in the dissemination activities and the main exploitable results is given in the following sections.

European dimension

The frame of the EU project allowed bringing multi-disciplinary expertise in universities, research centers and enterprises from different EU member states together in a complimentary manner to tackle the addressed challenges successfully and fostering EU wide collaboration. Both scientific and industrial partner benefited through the uptake of scientific achievements into business and the increase in interdisciplinary interaction to foster the generation of new knowledge. The project is so also contributing to the transition to a knowledge-intensive European industry. Especially the new plants concepts contribute to the move towards adaptive production in Europe. The results of the project – as outlined - will foster especially the competitiveness of European chemical and
pharmaceutical industry including SME and contributes to more sustainable European chemical production.

1.4.2 Main dissemination activities

Project contents and results have been disseminated by the project partners by about **250 activities** (a complete list is given in the A1 and A2 in Chapter 2.1). An insight in the main activities is provided in the following.

Naturally the main dissemination routes from academics and the R&D institutes in the project have been to publish project results in peer-reviewed journals and to contribute to scientific conferences. Remarkably, there have been a good range of central articles and contributions including also the industrial partners and thereby documenting the application orientation of the performed research and development works in the project.

**Overview and main journal contributions**

The project partners reported (see Table A1 in Chapter 2.1 for the complete list) about **40 publications** linked to project works in *peer reviewed journals* for the reporting period. Three more are submitted and about 7 planned for near future. Furthermore, one PhD thesis, two graduation reports, one master thesis and two book chapter are reported. Among the publications, there are several joint publications from project partners addressing main project topics and documenting the good interaction in the project. Good examples with regard to this are especially the publications the following publications dealing with cost analyses and life cycle assessments of the main chemical processes considered in the project:


Overview and main conference contribution

Project results have been reported in about 90 oral presentations including several keynotes and invited lectures. Supplemented has this been by about 50 poster contributions. All details concerning these dissemination activities can be found in Table A2 in Chapter 2.1.

The contributions have been given in a range of different conferences to reach the targeted audience. Among them have been the following:

- CHISA 2012 and 2014
- IMRET 12 (2012) and 13 (2014)
- ECCE 8 (2011) and 9 (2013)
- ISCRE 22 (2012)
- ACS National Meetings (2011, 2014)
- ProcessNet 2014
- 14th Int. Congress on Theoretical Aspects of Catalysis (Vlissingen, Netherlands, 2012)
- 3rd Int. Conference on Sustainable Pharmacy (Osnabrück, Germany, 2012)
- EUROPACAT X & XI (2011, Glasgow and 2013, Lyon)
- 15th International Congress on Catalysis (Munich, 2013)
- 10th Congress on Catalysis Applied to Fine Chemicals (Turku/Abo, Finland, 2013)

Joint activities with other EU FP7 projects

There have been a range of interactions and joint activities with other in parallel running EU FP7 projects. The highlights from these activities are a conference sessions during CHISA 2012 conference dedicated to EU FP7 projects and a joint booth during ACHEMA2012 fair.

The joint session of EU FP7 projects (F³ Factory, CoPIRIDE, POLYCAT, SYNFLOW and PILLS) took place during the CHISA 2012 conference in Prague (25.-29.08.12) with the following support from the POLYCAT project:

- Keynote lecture by *P. Löb, T. Rehm, V. Hessel, E. Sulman, L. Bronstein (IMM, TUE, TTU, INEOS): Novel polymer based catalysts and microflow conditions as key elements for innovation in fine chemical synthesis – the FP7 EU project POLYCAT

This special session had an audience of about 60 people including the PTA of the project Keith Simons. After project end, project partners supported a similar event during CHSIA 2014 in August 2014.

POLYCAT was represented also at the ACHEMA 2012 fair (18.-22.06.12) at the joint booth of the EU FP7 projects F³ Factory, CoPIRIDE, PILLS, POLYCAT and SYNCLEAN (see Fig. 37) organised by
DECHEMA. POLYCAT contributed via project posters, handouts, exhibits, a video provided by Evonik for repeated presentation on a monitor and via personal presence during the fair.

![Joint booth of diverse FP7 EU projects at ACHEMA2012 fair with POLYCAT participation (Source: IMM).](image)

Furthermore, P. Löb and T. Rehm from IMM joined the public dissemination event of the EU FP7 project SYNFLOW in 2014.

**Public Dissemination Event**

A public project dissemination event for the EU FP7 project POLYCAT entitled “Innovation in fine chemical synthesis by novel catalysts, continuous processing and novel reactor and plant concepts – Contributions of the EU Project POLYCAT” was organized. During this event, with the project approaching completion, the consortium wanted to share the highlights and what could be learned from the project especially for EU industries. The meeting took place on Tuesday 25<sup>th</sup> of March 2014 at Fraunhofer ICT-IMM, Mainz, Germany. Around 40 people from industry and academic took part in the meeting. Fig. 38 shows the program while Fig. 39 gives impressions from the event.
Dedicated events for students

There have been two special events dedicated to students. One summerschool-like event was realised in the context of the “2nd International Summer School - Catalysis for Sustainability - Exploring Resource Diversity for Energy & Materials Supply” which took place in Rolduc, Kerkrade, The Netherlands in June 23-26 2013. POLYCAT contributed by an own session but also by contributions to other joint sessions including the poster session. A report on the event with more information from POLYCAT perspective is posted on the POLYCAT public web site under the following link:


A report on the event as whole from the overall organisers is available under the following link:

Furthermore, the 6th POLYCAT General Assembly meeting taking place in Tver, Russia was taken as opportunity by TTU to organise on 16th April 2013 a “School-conference” for students of the university. The event was very well visited with about 200 students participating. Fig. 40 shows the program while Fig. 41 gives two impressions from the event.

**Fig. 40** Program of the “School-conference in the framework of 6th General Assembly meeting of FP7 project POLYCAT (CP-IP 246095)” organised by TTU in Tver, Russia on 14.04.2013.

**Fig. 41** Impressions from the “School-conference in the framework of 6th General Assembly meeting of FP7 project POLYCAT (CP-IP 246095)” organised by TTU in Tver, Russia on 14.04.2013 (Source: TTU).

**Other important dissemination activities**

- Public information about the CoPIRIDE project is accessible via the public web site http://www.polycat-fp7.eu/ which will be kept in operation over the next few years.
• **Evonik** reported in a **series of three articles** in different publications of Evonik about the Evotrainer concept and its linkage to the POLYCAT project:


### 1.4.3 Training and education in academic teaching

Aside the above mentioned main activities related to academic teaching (e.g. summer school, school conference), it is worth mentioning that POLYCAT project results found albeit not direct project content their way into training material/courses at least at TU/e.

### 1.4.4 Exploitation of results

This chapter lists in view of commercial potential main project results. Rather an insight than a complete summary is given due to confidentiality reasons and sensitivity of commercialization plans. First an overview regarding generated patent applications and then an overview over from the partners identified main exploitable results is given.

**Patents**

Project works and results led to **2 patents and 2 published patent applications**. The patents/patent applications **protect** either the **preparation of novel catalyst systems from POLYCAT** (in case of UNEW: NSMP materials and in case of INEOS: catalytically active magnetically separable nanoparticles) or the **application of POLYCAT catalysts to specific reactions** (HPS of TTU to selective oxidation of D-glucose and oxidation of lactose). Some more details are given in Tab. 3.

**Tab. 3** List and details of published patents / patent applications resulting from POLYCAT project works.

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<tr>
<th>Type of IP Rights:</th>
<th>Embargo date</th>
<th>Application reference</th>
<th>Subject or title of application</th>
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Exploitable project results

The topic of exploitation of project results have been continuously followed and discussed during the complete project runtime e.g. by a first exploitation plan already in the proposal stage, by discussions during the Exploitation Strategy Seminar held in April 2012 and by consideration at the end of the project.

Besides the general advancement of knowledge generated in general especially by universities and research organizations which are not pointed out here but are naturally also of high relevance and importance, the following exploitable results have been identified and characterized finally:

- Plant concept in container-format for fine chemistry / pharmaceuticals productions, i.e. ECoTrainer (Evonik Industries AG). Exploitation e.g. by Evonik internal use as tool to reduce time-to-market and reduce investment risks and via licensing of container design as currently in negotiation with Fraunhofer ICT-IMM.

- CNT/NCNT supported catalyst like e.g. Ru/NCNT and Ni/NCNT or NCNT as metal free catalyst for a range of organic reactions including continuous processing approach (BTS).

- Novel flow catalytic reactor matching customer needs and matching existing modular microreactor system platform of EMB (EMB).

- Novel flow catalytic reactor compatible with basic modular system of ThalesNano (TN).

- Application of Atomic Layer Deposition methodology and apparatuses to new areas: coating of microreactor parts and deposition of heterogeneous catalysts on surfaces (PICOSUN).

- Ru/HPS and Pd/HPS as catalysts for general use but especially for glucose hydrogenation, alkylnol reduction and Suzuki coupling reactions. (CLARIANT).

- New catalytic microreactors for development purposes and production (Fraunhofer ICT-IMM).
### 1.5 Contact details

#### 1.5.1 Project coordination

Coordinator: 
**Fraunhofer ICT-IMM** (which emerged 01.01.14 from the Institut für Mikrotechnik Mainz GmbH, IMM)

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#### 1.5.2 Project consortium

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