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Disruptive technology for fine chemicals synthesis with catalyst-coated tube reactors

KEYWORDS: Catalysis, tube reactors, coating, fine chemicals.

ABSTRACT

Catalyst-coated tube reactors have the potential to halve the manufacturing costs across the fine chemicals industry. The technology delivers high mass and heat transfer rates in reactions providing higher reactor utilization and efficiency promising to disrupt this industry. The reactors can be applied to a wide range of catalysts covering more than 90% of the needs of chemical industry in manufacturing of nutraceuticals, agrochemicals, flavours & fragrances and speciality chemicals.

RECENT TRENDS IN FINE CHEMICALS MANUFACTURING

Fine chemicals represent a wide range of compounds used as vitamins, drugs, fuel additives, dyes, fragrances, agrochemicals and many others. Only agrochemicals (including animal food supplements), as well as flavours & fragrances (F&F), contribute to a substantial share of the world's fine chemicals production. The market for fine chemicals was worth €700 billion in 2015. As the population grows, the need for agrochemicals and F&F speciality chemicals will be increasing. Within developing countries, the market of animal food supplements is projected to increase rapidly over the next few decades (average 10% per year) mainly due to the standard of living increase. The synthesis of fine chemicals nowadays relies almost exclusively on the batch reactor technology. Batch reactors allow multi-product manufacture from a single unit, which significantly reduces the initial capital cost of plants. Batch synthesis has high manufacturing costs due to ample repetitive non-productive operations, high safety infrastructure costs to address the possible risk of explosion, poor reaction control that results in decreased product quality and yield combined high solvent and energy consumption. Also high market delays costs are common that are related to the difficult scalability. Incremental improvements in the batch technology are exhausted requiring a new disruptive technology.

One of the latest megatrends in fine chemicals manufacturing is continuous processing, and in particular, the substitution of traditional batch processes with continuous processing. According to Lawrence Yu, the US Food & Drug Administration's Deputy Director, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, "we are entering an era of precision medicine, when drugs must be made with unique features and provided more quickly to patients in need. FDA will continue our efforts to encourage the advancement of continuous manufacturing" (1). Continuous synthesis is recognized as the technology that would enable and even boost process intensification to develop safer, more efficient, and cleaner chemical processes (2, 3). The key change driver is the need to achieve cost savings, improve product quality and process sustainability. About 25% of all drugs on the market contain amide bonds, and the amide synthesis covers 65% of drug candidates (4). Catalyst design is an important tool to improve the performance of structure-sensitive reactions. Control of the spatial distribution of active sites within the catalyst support, metal dispersion related to the particle size and catalyst texture are important parameters to tailor the catalyst design (5).

DIRECT AMIDE SYNTHESIS IN FLOW REACTORS

Coupling reactions are a widely used in chemical and pharmaceutical industries. About 25% of all drugs on the market contain amide bonds, and the amide synthesis covers 65% of drug candidates (6). Despite the amide formation being a key reaction in organic chemistry, the direct amide synthesis reaction is little used and little explored. Acceptance of the feasibility of this reaction depends upon the development of both a convenient flow reactor technology and the design of active catalysts, which can promote the reaction at relatively mild conditions at short contact time is flow. Recently, we developed a series of core-double shell composites ($TiO_2@SiO_2@NiFe_2O_4$) with an intermediate silica layer for direct amide synthesis, which is one of the most important reactions in pharmaceutical industry. The catalysts have been employed in a fixed bed tubular reactor in a direct amide synthesis reaction between aniline and phenylbutyric acid at 150 °C (Figure 1) (7). The intermediate silica layer of the catalyst increased the porosity of the outer titania layer. The initial reaction rate increased by 61% as compared to a similar core-shell $TiO_2@NiFe_2O_4$ catalyst (8). However the non-uniformity in catalyst bed porosity along parallel reactors could lead to a variation in the flow rates over them and a decrease in the overall reactor performance. Therefore stable, uniform, and reproducible catalytic coatings are required for the reproducible operation on the level of multiunit operation, when several reactors are connected in parallel to increase their productivity.

NOVEL CATALYTIC COATINGS FOR GAS-LIQUID REACTIONS

Conventional selective heterogeneous catalytic hydrogenation involves three phases, where the reaction between gas and liquid reactants occurs on the surface of a porous solid catalyst.

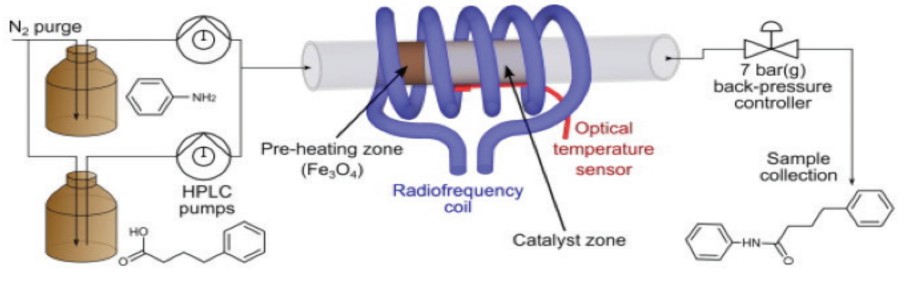


Figure 1. Schematic view of direct amide synthesis reaction in a flow reactor.

Such three-phase processes are severely restricted by limitations in mass transfer between gas and liquid as well as in heat transfer between the solid and the surrounding affecting reaction rate, selectivity. Catalyst-coated tube reactors were shown to provide an efficient solution for continuous flow manufacturing in gas-liquid-solid catalytic reactions making it possible to develop and synthesize new chemical compounds and scale up to 10 kg/day production and, with an additional scale-up step up to 100kg/day (9-13). A novel sol–gel-based method was reported for the synthesis of metal oxide and carbon coatings suitable for long millireactors. The method is similar to the static coating method, but uses elevated temperature and introduces an additional control parameter, the displacement speed that controls the coating thickness (13). The coating apparatus consists of a stepper motor, controlled by a microcontroller, which pushes the tube, filled with catalyst precursors, vertically at a constant velocity into an oven (Figure 2). The tube is guided into the oven by a copper tubing of a larger diameter insulated for the first 5 cm that allows gradual temperature increase along this length. After the process, the coated tubing was left at 200°C in a vacuum oven to stabilize the coating.

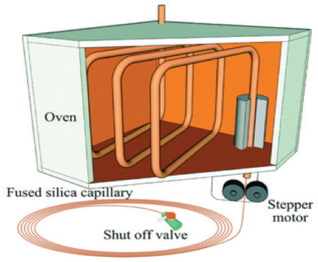


Figure 2. Schematic view of the coating apparatus.

Limited scalability of the packed bed and batch reactors require substantial efforts into the process development and scaling up that result in the high market delay costs. The continuous synthesis in the catalyst-coated tube reactors eliminates the majority of the non-productive operations pertinent for batch processes. The strongly immobilized catalysts eliminate fouling, the major problem in slurry and packed bed problems, and allow for stable operation for hundreds of hours (Figure 3). Low pressure is required to pump the substances providing high energy efficiency. Moreover, the small reactor volume provides an excellent intrinsic safety decreasing the safety infrastructure costs. This platform technology has the potential to bring a game-changing flow design into the mainstream of fine chemical processing because of high mass and heat transfer rates in reactions providing higher reactor utilization and superior operational parameters, thus reducing manufacturing costs.

DEMONSTRATION IN FINE CHEMICALS SYNTHESIS

Highly selective hydrogenation of cinnamaldehyde to cinnamyl alcohol in tube reactor (i.d. 0.53 mm, o.d. 1.6 mm) coated with a Pt/SiO_2 catalyst was demonstrated (9). A 90% selectivity towards the unsaturated alcohol was obtained at the aldehyde conversion of 98.8%. This is a six-fold improvement in the selectivity compared to a batch process where acetals were the main reaction products. In another example, selective hydrogenation of 2-methyl-3-butyn-2-ol (MBY) was studied in a tube reactor coated with a 5 wt.% Pd/ZnO catalyst (10). MBY hydrogenation is one of the key reactions that is used in the synthesis of vitamin E intermediates and represent a range of alkynol molecules that are widely used in vitamin, fragrance, and pharma areas (Scheme 1). The catalyst-coated tube reactor with the Pd/ZnO catalyst allowed to achieve an excellent selectivity towards the intermediate alkene of 97.8 % at an ambient H_2 pressure and a reactant conversion of up to 90%. A very high turn-over number of 100,000 was observed over the coated catalyst (10). The catalyst tube reactors with the Pd/ZnO catalyst allowed a throughput of above 4 kg a day in a single 5 m long 1.5 mm diameter reactor in the solvent-free MBY semihydrogenation (12). The introduction of a second metal into the catalyst coating facilitates the fine tuning of the oxidation state of Pd nanoparticles, that is the main factor responsible for their catalytic properties (14). The application of a bimetallic $PdBi/TiO_2$ catalyst with a Pd/Bi molar ratio of 11 in a catalyst coated tube reactor improved the product yield to 90% and further to 95% in the presence of 10 mol.% pyridine in the reaction mixture in the MBY semihydrogenation (11). The highest yield of MBE (94%) was achieved over $Pd_{50}Zn_{50}/TiO_2$ coatings at a conversion of 99%, a temperature of 313 K, and a partial hydrogen pressure of 1 atm (15).

For many applications in fine chemical industry, the development of a small scale direct synthesis process for production of ultra-pure grade hydrogen peroxide in desirable concentrations

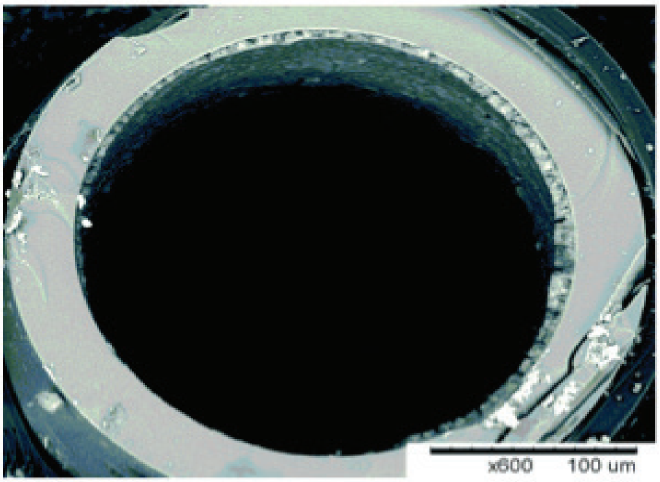
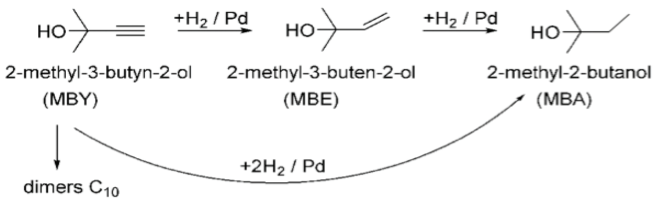


Figure 3. A cross-sectional SEM image of a catalyst-coated tube reactor showing a 4 mm thick mesoporous titania coating.



Scheme 1. Hydrogenation of 2-methyl-3-butyn-2-ol (MBY).

without the addition of stabilizers and preservatives represents a significant interest, as it avoids the risks of transportation and storage of large amounts of hydrogen peroxide. The direct synthesis of hydrogen peroxide over Au-Pd/TiO_2 catalysts coated onto the inner channel walls was demonstrated by Paunovic et al. (16, 17). These authors used a two-step approach for coating deposition. At first, a silica coating was prepared by sol-gel method. Then the silica layer was functionalized with an Au–Pd bimetallic clusters dispersed in an organic solvent. Finally after removal of the organic solvent, the catalytic layer was dried and calcined at 380°C to obtain a porous coating. The typical relative deviation in coating thickness was ≤20%. The authors studied the direct H_2O_2 synthesis under two phase flow conditions. The role of the liquid phase was to collect and dissolve the hydrogen peroxide, since it is highly unstable and decomposes to water and oxygen. The maximum H_2O_2 yield was achieved at an H_2/O_2 molar ratio of 1.

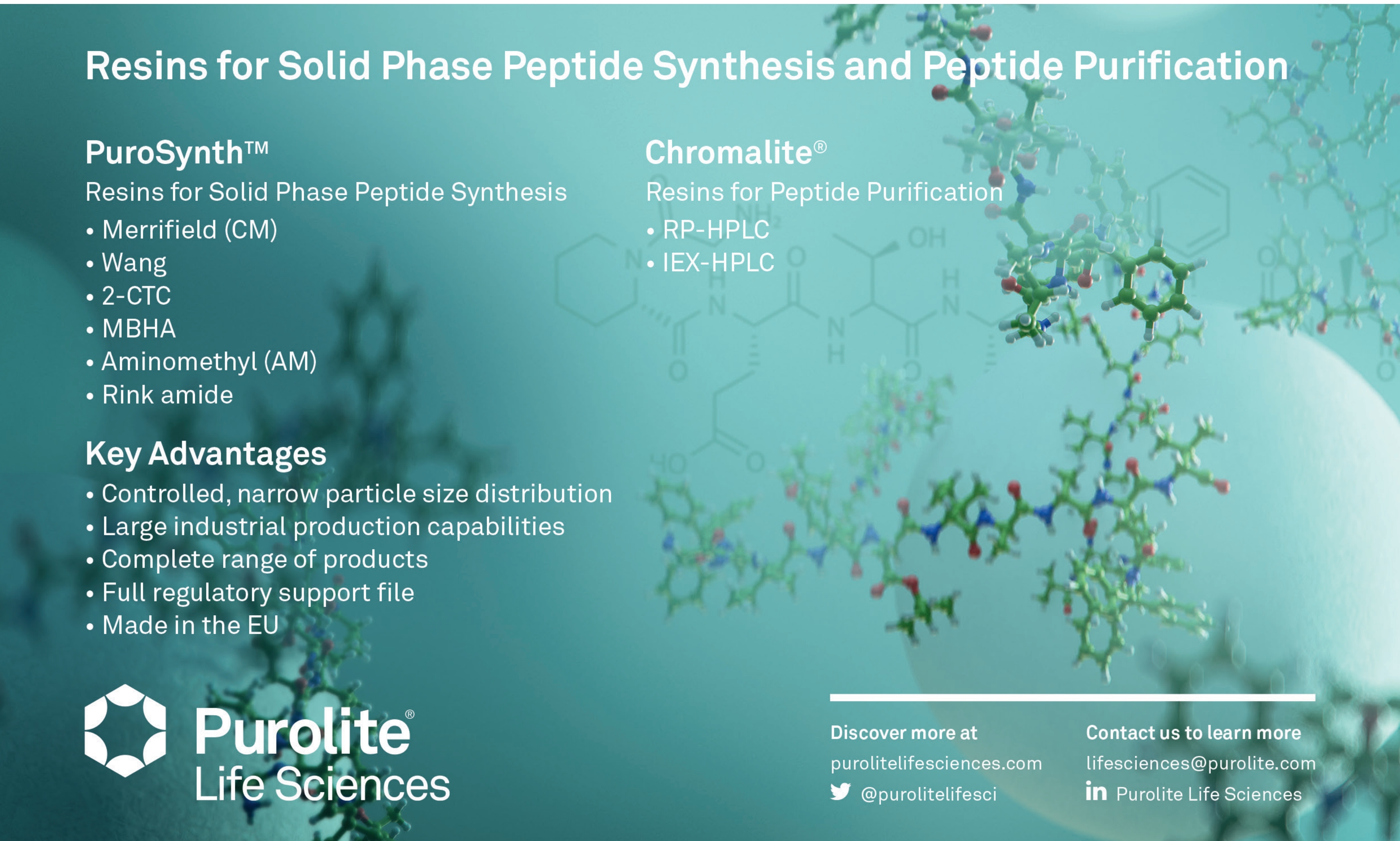
REACTOR SCALE-UP

The high rates of mass and heat transfer (18), minimum axial dispersion and the high interfacial area allow millichannel reactors to run highly exothermic reactions safely, permitting greener routes for processing. A single catalyst coated tube reactor can provide a product yield of typically 1-10 kg/day. It was reported that at a reaction pressure of 50 bar, the throughput of about 1.5 kg/day can be reached in a 5 m reactor with a diameter of 0.5 mm operated at a pressure drop of 7 bar (12). The pressure drop can be decreased by increasing the reactor diameter to 1.5 mm, allowing for longer reactors (30 m) and higher throughputs reaching up to 28 kg/day. Thus catalyst-coated tube reactors seem particularly promising for the pharma industry allowing for quick scale up from gram to kilograms in the same reactor.

In order to increase the production capacity even further, several reactors should be connected in parallel (19, 20). The exact number of microchannels depends on the maximum allowed pressure drop over the reactor and the channel length which is often limited by hydrogen consumption rate (Figure 4). Distributing gas and liquid flows in parallel channels can be achieved via branching, internal distribution (like in the monolith), or by using separate gas and liquid feeding for each parallel channel (21). When additional hydraulic resistances are placed between the single phase flow distributor and the gas and liquid feeding sections gas–liquid channeling is prevented and the flow uniformity is maintained within 10% for different reactor geometries and dimensions as well as for is different viscosities, surface tensions and the flow rates for six different fluids studied. The effect of flow maldistribution on selectivity depends on both the mass transfer rate and reaction kinetics (22). The deviation in selectivity with flow distribution is generally greater in the case of the mass-transfer-limited regime, which cannot be realized in the tubular reactors with a diameter of 1.5 mm.

OUTLOOK

In addition to small and medium scale production of fine chemicals, the catalyst coated tube reactors can be used for fast catalyst screening. The coating method allows to deposit different catalyst compositions (in terms of metal loading and dispersion, porosity and the ratio between different metals) in a very reproducible way. For example, the metal ratio in the bimetallic nanoparticles can be varied by changing the ratio of metals in the catalyst precursors. The porosity and the coating thickness can be changed by the displacement speed and the furnace temperature. Typically, the thickness of the catalytic layer needs to be carefully adjusted in such a way that the reaction kinetics can keep up with the fast external mass transfer, while diffusion limitations through the layer deposited need to be minimized to use all the catalyst available. When supporting catalysts on metal structures, care must be taken that the reactor material and catalytic coating are compatible (23).



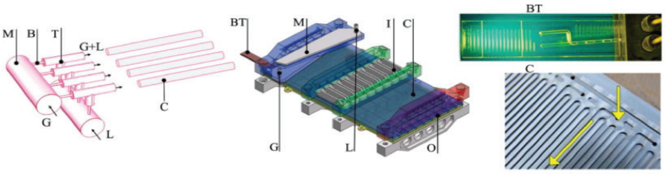


Figure 4. Left, schematic view of a barrier-based gas–liquid flow distributor for four parallel milli-channels. Center, a CAD view of the barrier-based gas–liquid flow distributor showing its components. Right, the enlarged view of the barrier channels etched in a chip. Symbols used are: (G) gas inlet, (L) liquid inlet, (M) manifold, (B) barrier channels, (T) T-mixer, (C) reaction channels, and (BT) barrier-mixer chip, (I) inspection window, and (O) collector block

Aluminum, molybdenum, Fecralloy, and similar alloys, and stainless steels are routinely coated with catalytic coatings. Low mechanical stability of catalytic coatings is a major drawback of the technology. The adhesion of the coatings can be improved by deposition of an additional hydrophilic layer (23). To handle the catalyst regeneration problem, the deactivated catalysts can be removed from the tubes by pumping a removal solution and fresh catalysts can be coated onto the same tubes. The metal leaching, being another major drawback, can be significantly decreased by obtaining strong metal-support bonds in the deposition process and by the addition of second metal which would stabilize the noble metal on the surface.

The catalyst mass can be increased by increasing the channel length if the thickness of the catalytic layer is a limiting factor. When several tubes are connected in parallel, large array of catalyst performance data can be obtained within a time of just few minutes. The uniform flow distribution among different tubular reactors guarantees high reliability of the data collected. In the absence of dry zones, that are often observed in packed bed reactors, the reactors operate in kinetic mode due to very high heat and mass transfer rates.

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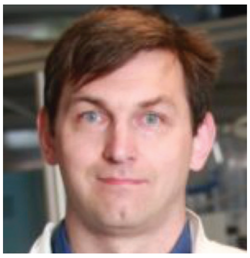

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