**Process intensification in direct amide synthesis with catalytic packed-bed milli-reactors operated under induction heating**

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**Highlights**

* Induction heating improved catalytic activity by 1.5 times in a direct amide synthesis reaction.
* The initial reaction rate over core-shell catalysts was further increased by 1.7 times r as compared to a mechanical mixture.
* Thermal gradients in a packed bed milli-reactor under RF heating have been analyzed.
* Design criteria for a near-isothermal milli-reactor have been suggested.

**1. Introduction**

The fact that small-scale and distributed chemical manufacturing systems are proved to offer advantages such as lower capital expenses, compactness of equipment, relatively small energy consumption, and reduced by-product formation has led to the growing interest in newer process intensification methods using reactors with channel diameter in the millimeter range (milli-reactors). These reactors can be heated by induction heating of magnetic microparticles placed inside the reactor to generate heat rapidly and uniformly within the bed, while eliminating hot spots and large radial temperature gradients. Induction heating utilizes easier scalable hardware such as magnetic materials and induction coils connected to an RF generator.

Under RF heating, the composite magnetic catalyst should provide both high heating and reaction rates. A core-shell structure is often used because the shell layer often acts as a catalyst and protects the magnetic core from chemical erosion and aggregation. Over the last few years, we developed a series of core-shell composites for direct amide synthesis, which is one of the most important reactions in pharmaceutical industry [1-3]. The catalytic activity was determined in a reaction between aniline and phenylbutyric acid in a fixed bed flow reactor under induction heating.

**2. Methods**

The catalytic activity was compared in the reaction between 4-phenylbutyric acid and aniline. A glass reactor (Omnifit HiT, i.d 6.6 mm, 250 cm long) was used. Two HPLC pumps were used to feed the solutions of 4-phenylbutyric acid and aniline in p-xylene to the reactor. The flow reactor was packed with the catalyst pellets (fraction size: 125–250 m) and it was placed in the center of an 8-turn RF coil operated at 300 kHz. A 5-mm preheating zone was packed with Fe3O4 pellets of the same size. A fiber optic temperature sensor was attached to the outer surface of catalytic zone to control the temperature using a PID controller.

**3. Results and discussion**

Under near-isothermal conditions, no products other than the amide were identified [3]. The reaction kinetics is the first order in respect to both amine and acid and it is controlled by strong product inhibition at conversion levels above 50%. However, even a small deviation of the catalyst temperature from an isothermal operation results in a substantial decrease of selectivity. Because of their small dimensions, larger contributions of axial conduction and heat losses to the environment were observed in the millireactor and, accordingly, the temperature profiles deviate from those observed in large-scale reactors that follow adiabatic operation. Therefore we developed quantitative criteria for the absence of axial temperature gradients in the reactor [4].

The method was applied to control the temperature in the reactor. It was necessary to split up the catalytic bed in several heating sections with additional sections of nonmagnetic catalyst in order to obtain near-isothermal conditions. One nonmagnetic catalytic zone and one heating zone with composite magnetic catalyst forms a single periodic unit that is repeated in the axial direction. Further adjustments were made by varying the position and the length of the individual heating zones. The approach allows to obtain a temperature non uniformity inside the catalyst bed within 2K.

Under isothermal operation, the induction heating resulted in a higher reaction rate as compared to conventional heating. Furthermore, the initial reaction rate was 1.7 times higher over the composite catalyst as compared to the mechanical mixture of the same composition without major changes in the deactivation kinetics. This indicates the importance of the close contact between the magnetic core and the catalytic shell in the composite catalysts. The initial reaction rate decreased by 36% after a period of 55 h on stream. The catalyst activity was restored after a treatment with a H2O2 solution.

**4. Conclusions**

Determination of the temperature profile in an RF-heated catalytic packed-bed milli-reactor is essential for interpretation of kinetic data in these systems. The short distance between the heating source and the catalyst provides an excellent temperature uniformity, and decreases heat losses which are the main problems in conventional heating. This, together with the possibility of fast plant startup, holds promise for these reactors to replace classical batch reactors as well as to be used as remote chemicals plants in a future economy driven by electricity obtained from sustainable energy sources.

**References**

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