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# Biphasic liquid-liquid reactions

Dr Robert Pestman of Flowid and Jovan Jovanovic of the Eindhoven University of Technology look at how micro flow chemistry can be applied to biphasic systems

Reactions in biphasic systems consisting of two immiscible liquid phases have a wide variety of applications. Three examples of the broad range of reaction classes are as follows.

First are reactions in an organic phase that are catalysed by a water-soluble catalyst. These can be (Lewis) acid-catalysed reactions, such as Diels-Alder reactions, aldol reactions and Friedel-Crafts reactions or hydroformylations.<sup>1-3</sup>

The advantage of these processes is that the catalysts can readily be recycled by phase separation after reaction. A major drawback, however, is that even energy-consuming vigorous stirring cannot bring both phases sufficiently in contact to attain fully efficient use of the catalyst.

Another is a combined extraction-reaction process, during which one of

the products is extracted to another phase, for example dehydration reactions in which the dehydrated product is extracted by an organic phase, thus avoiding back and side reactions.<sup>4</sup>

The advantage here is that, theoretically, the desired product is separated instantaneously from the reaction phase. In this way, the equilibrium is shifted in the desired direction and undesired consecutive reactions are avoided. In practice, however, extraction is not as fast and complete as desired.

Finally, there are reactions between two reactants of which one is only water-soluble and the other is only soluble in an organic solvent, for instance in the nucleophilic substitution of a haloalkyl with sodium cyanide.<sup>5</sup> These reactions are often facilitated by a phase transfer catalyst (PTC).<sup>6</sup>

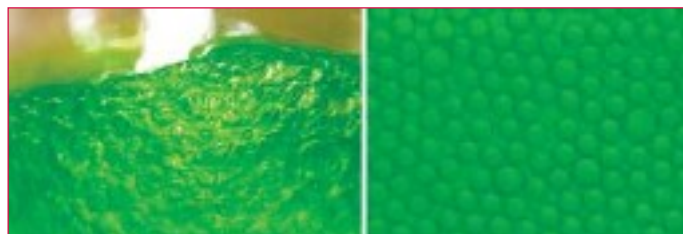


Figure 1 - Droplet distribution with traditional batch reactor (a) & micro flow reactor (b)

In all of these types of reactions, the reaction rate is limited by the transfer of reactants or catalyst from one phase to the other. This results not only in a slow, mass-transfer limited reaction but also in a low selectivity, as other, undesired reactions are often not limited in the same way. A high interfacial area is thus needed for an optimal reaction performance.

In traditional batch reactors, an interfacial area as high as possible is obtained by vigorous mechanical stirring, which requires high energy consumption. The liquid droplets created in this way differ significantly in size and are not distributed evenly over the reaction mixture. The result can be hot spots and low product quality.

## Micro flow reactors

An increasingly popular class of new reactor concept is micro flow reactors. These have a number of important advantages, not least those arising from their small dimensions: good heat transfer and thus easy temperature control; no mass transfer limitations; and, low safety risks.

In addition, micro flow reactors have, as the name suggests, the characteristics of a flow reactor. In these, the reaction time is controlled accurately by the residence time of the materials in the reactor. This means that a reaction does not have to be run to complete conversion; if desired, high yields of an intermediate product can be obtained simply by reducing the residence time.

Another benefit of flow reactors is that the reactant, the intermediate and the product are physically separated in the beginning, the middle and the end of the reactor respectively. This suppresses side-reactions and can lead to significantly higher selectivities. Last but not least, a great advantage

of flow systems is their ease of scale-up compared to batch systems, since mass and heat transport remain the same or are easily predictable during scale-up.

Another less-known advantage of micro flow reactors is used for optimising biphasic liquid-liquid reactions. This gives the possibility of creating well dispersed biphasic liquid-liquid systems with a high interfacial area. Flowid has developed considerable experience in significantly optimising biphasic reactions through the application of micro flow reactors.

## Biphasic reaction

As mentioned above, stirred batch reactors have non-uniform dispersed droplets (Figure 1a), leading to a non-optimal interfacial area. By using a continuous flow reactor with a static micromixer, in contrast, a reaction mixture can be obtained with droplets that are evenly distributed and have a homogeneous size distribution (Figure 1b).

A far higher interfacial area between the two immiscible phases can thus be achieved in micro flow systems. The interfacial areas in a micro flow reactor range from 10,000 to up to 200,000  $\text{m}^2/\text{m}^3$ , whereas industrial batch reactors can achieve maximum interfacial areas of 1,000  $\text{m}^2/\text{m}^3$ .<sup>7</sup>

The advantages of the use of micro flow reactors in biphasic systems have already been noted by others.<sup>8,9</sup> To exemplify the benefits of a biphasic reaction in micro flow reactors, we have chosen a PTC reaction of sodium benzoate with benzyl bromide to benzyl benzoate (Figure 2). Benzyl bromide is a hazardous reactant with lachrymatory (tear gas) properties. Therefore, operational safety in production is essential. The product is commonly

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### DAIKIN CHEMICAL EUROPE GmbH

Immermannstr. 65D 40210 Dusseldorf, Germany  
TEL: +49-211-179225-28 FAX: +49-211-1640732

### DAIKIN AMERICA, INC.

20 Olympic Drive Orangeburg, NY 10962, U.S.A.  
TEL: +1-845-365-9500 Toll-Free: +1-800-365-9570  
FAX: +1-845-365-9515

## DAIKIN INDUSTRIES, LTD.

Osaka Japan Phone: +81-6-6373-4221 FAX: +81-6-6373-4390  
URL: <http://www.daikin.co.jp>

Daikin America, Inc. URL: <http://www.daikin-america.com>  
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