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Fluidic separation in microstructured devices – Concepts and their Integration into process flow networks

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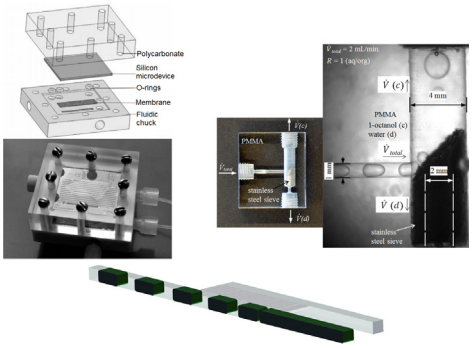
HIGHLIGHTS

- Flow patterns in liquid-liquid micro-flow.
- Liquid-liquid microfluidic dispersion and phase separation.
- Applications in the field of microextraction.
- Countercurrent-flow liquid-liquid processing.
- Integration of flow separation into process flow networks.

GRAPHICAL ABSTRACT



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ABSTRACT

FDA and pharmaceutical industry turn the vision of integrated end-to-end manufacturing currently into reality. Accordingly, besides the efforts to develop reactions in continuous flow, it is also essential to consider separation of reaction mixtures and purification of the desired product - and how these are best integrated into a process design. In this context, the coupling of flow reactors and flow separators as well as coupling of different flow separators, regarded as hybrid processes, are considered. This review shows current successful developments on fluidic separation units and their integration in process flow networks, in which reactors and separators are connected. The review also gives developments on countercurrent-flow separation units, which are necessary for highly-efficient, continuous processing. Such multiple equilibrium steps are necessary, but hard to achieve for small flow rates.

1. Introduction

The majority of research in micro-process technology were so far focused to one or few reaction steps with the separation done offline (Hessel and Löwe, 2003; Hessel et al., 2014, 2013; Jähnisch et al., 2004; Wiles and Watts, 2008). However, the development of microfluidic separation units is still very limited. These microfluidic separation units have been mainly investigated for analytical and synthetic purposes, often with a single thermodynamic equilibrium step. There are, however, relatively limited amount of micro separation devices developed for chemical purposes. From about 2011 onwards, they are increasing in number (Kenig et al., 2013). Their current application examples are limited, but offer great potential for added benefits to be implemented in flow networks as well as if used on their own. Flow separators show dynamic development in recent years and we will give update focus here. These devices are mainly liquid-liquid extraction units. Recently, several distillation (Hartman et al., 2009; Lam et al., 2011; Sundberg et al., 2009; Ziogas et al., 2012),

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absorption (Gao et al., 2011; Niu et al., 2009; Ye et al., 2012) and chromatography (Culbertson et al., 2000; Jemere et al., 2009; Tran et al., 2010) units were also developed. Here the focus is given on microextraction. For review on other flow separation units the reader can refer to previous review papers (Hessel et al., 2012; Kenig et al., 2013).

Most flow separation units developed have been characterized as stand-alone tools, i.e. without connection to a flow reaction device. To achieve a process flow network, the coupling of microfluidic separation units with microreactors is required. So far, there are only few demonstrations for this. Since the development of multiphase flow reactors is well documented in review papers, it is not considered as such in this review paper. Rather the flow separation units are given the spotlight. Furthermore, most of the application examples of flow separation units were given for lab scale. For pilot-scale applications, flow separation units that can handle high throughput are required and this was rarely studied (Cervera-Padrell et al., 2012; Vural Gürsel et al., 2016). In the review paper besides others information of the maximum flow rate achieved in the application examples will be provided.

In pharmaceutical industry the vision of an end-to-end continuous manufacturing starts to become reality and the self-determined time limit is the year 2025 (Brennan, 2015; Chatterjee, 2012; Promoting Continuous Manufacturing in the Pharmaceutical Sector, Discussion Guide, 2015). This is due to strong efforts of the ACS Green Chemistry Institute Roundtable, which is a platform for the pharmaceutical industry and the legislation authority FDA. FDA has for the first time approved a company switching production of a drug from batch to continuous manufacturing. The switchover from batch to the new technology for the production of the HIV drug Prezista takes place in a plant of Janssen Company in Gurabo, Puerto Rico (Palmer, 2016). Another manufacturer, Vertex, has installed continuous manufacturing for the cystic fibrosis drug Orkambi (lumacaftor/ivacaftor), since its approval date in July 2015 (Palmer, 2016). Besides drug organizations such as PDA (Bowen, 2015) and pharmaceutical companies such as Novartis (Novartis-MIT Center for Continuous Manufacturing, 2016), major players on the processing and process control side have committed to the continuous manufacturing such as Siemens (Siemens, Continuous Manufacturing, 2016) and GEA (GEA, Continuous Manufacturing, 2016). A company dedicated to just this business has been launched by MIT and Novartis, named Continuus (Continuus Pharmaceuticals, 2016).

FDA's encouragement of the development of emerging manufacturing technology for improved product quality and availability has meanwhile been institutionalized. An own group within FDA's CDER (Center for Drug Evaluation and Research) has been formed, named the Emerging Technology Team, ETT (FDA's Emerging Technology Team (ETT), 2016). The ETT shall work in partnership with relevant pharmaceutical quality offices and assume a leadership or co-leadership role for the cross-functional quality assessment team. They will address pre-submission questions and proposals about the use of specific emerging technology submitted by pharmaceutical companies.

Crucial part in continuous manufacturing is an integrated process flow network ('microreactor networks') which can be seen as the biomimetic-technological equivalent of nature's 'factory compartmentalization' (Jones et al., 2011). The organelles of the cell mediate a continuous series of highly regulated catalytic cascades as efficient 'biochemical assembly lines'. These cascades serve as metabolic pathways for generating complex molecular scaffolds (Kaelin and Thompson, 2010) and signaling pathways for process control (Ingham et al., 2011), e.g. the menaquinone and the futalosine cascades (Begley, 2006) and the tissue factor pathway for blood coagulation (McVey, 1999), respectively.

Countercurrent-flow separation processes are ubiquitous in conventional process technology and are often driven by gravity and density differences of the participating phases. With smaller dimensions and internal volumes, gravity forces diminish and surface forces become important. In channels and tubes below 3 mm internal diameter approximately, slug flow is formed and serves for high interfacial area for improved mass transfer. This contribution describes the typical flow regimes of two immiscible liquids in small scale devices for extraction purposes. The main part of this review treats the important steps of droplet generation and phase separation followed by typical applications. The final chapters deal with countercurrent-flow separators for improved efficiency and successful applications.

2. Liquid-liquid flow regimes

In liquid-liquid flow systems, with the use of different mixing elements and conditions (e.g. velocity of the phases, velocity ratio of the phases, physical properties of the phases) different flow patterns are observed (Kashid et al., 2007). The most common flow patterns observed in microcapillaries are parallel flow, slug flow, and dispersed flow (Fig. 1).

Due to small size of the systems, the surface forces become dominant with the interfacial tension, and viscous and inertial forces acting as competing forces. Several authors studied mapping of the flow regimes in terms of dimensionless numbers to define quantitatively the influence of different forces. Dessimoz et al. (2008) made flow transition maps based on Capillary

$$Ca = \frac{\mu u}{\sigma} = \frac{\text{Viscous force}}{\text{Interfacial tension}} \tag{1}$$

with mean velocity u, dynamic viscosity μ, and interfacial tension σ, as well as the Reynolds number

$$Re = \frac{\rho u d_h}{\mu} = \frac{\text{Inertial force}}{\text{Viscous force}} \tag{2}$$

with hydraulic diameter d_h and density ρ. Zhao et al. (2006) proposed to use the Weber number

$$We = \frac{\rho u^2 d_h}{\sigma} = Re \cdot Ca = \frac{\text{Inertial force}}{\text{Interfacial tension}} \tag{3}$$

for the mapping of the flow patterns to express whether interfacial tension or inertia is the dominant force. Capillary number shows the ratio of viscous force to interfacial tension force and it is directly proportional to velocity. Weber number gives the ratio of inertia

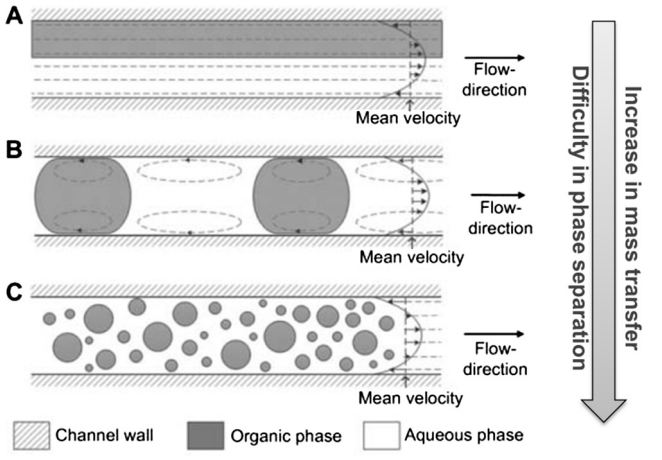

Fig. 1. Liquid-liquid flow patterns in microchannels (adapted from Holbach and Kockmann (2013)); (A) parallel flow; (B) slug flow; (C) dispersed flow.