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Stabilisers for water-in-fluorinated-oil dispersions: Key properties for microfluidic applications

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ABSTRACT

Droplet-based microfluidics appears as a key emerging technology for the miniaturization and automation of biochemical assays. In terms of technology, it stands on two basic pillars: microfluidic devices on the one hand and emulsions on the other hand. Huge progress has been made on large scale integration of devices and batch production of devices. The limiting factor for a full application of the technology is actually not device development, but rather the robust control of emulsion formulations to be used in these devices. We here review the basic problems related to emulsions relevant for microfluidic applications and open up on new promising applications for these systems.

1. Introduction

Simple liquids do not necessarily mix. It reflects the fact that various compounds interact differently at the molecular level. However, immiscible liquids transiently exist in mixtures in the form of dispersions. An emulsion, is a dispersion of small droplets into a continuous phase, stabilised by a third compound, typically surfactant molecules [1]. The properties of the resulting mixture – mechanical, rheological, chemical – are essentially different from those of both individual liquids, creating complex fluids of practical interest for applications. Many products of our daily life are based on these disperse systems, from food colloids to pharmaceutical and cosmetic formulations, drug delivery systems, to just cite a few applications [2]. The kinetic stabilisation of dispersions is essential to maintain the properties of the mixture over time. Recently, the enormous potential of emulsion droplets as miniaturized reaction vessels has been exploited to provide novel assay systems [3,4]. Interestingly, the idea of using droplets as microreactors has already been brought up in the middle of the 20*th* century [5]. The real breakthrough came with the recent advances in the droplet-based microfluidic technology [6–11]. Droplet-based microfluidics emerged at the very beginning of the 21*st* century as a subdomain of microfluidics [6]. It employs immiscible phases that are flowed through microchannels such that homogeneous shearing of the liquids results in the formation of emulsions with discrete monodisperse droplets. The technique allows for the production and precise manipulation of calibrated emulsion droplets at high rates (up to several kHz), unleashing an enormous potential for high-throughput screening applications, single cell analysis, DNA-based diagnostics or drug screening [12–19].

The emulsions produced in microfluidics are unconventional from a material point of view: each droplet has typically an individual composition at every time step, depending on the initial loading of compounds and on the biochemical processes taking place in the droplet (Fig. 1(A)).

As a result, new types of ageing mechanisms are to be expected in these emulsions. First, the flow of droplets in microchannels affects the stability of the droplets (Fig. 1(B)), and induce ageing of the emulsion by manipulation of individual droplets [22,23,21]. Understanding and controlling these ageing processes are a prerequisite for an efficient use of the technology [11]. It is therefore important to understand the dynamics of surfactant-laden interfaces on the flow of droplets in confinement, at the time-scale of droplet manipulation (typically ~1 ms) and at the lengthscale of the microchannels (typically 1–100 μm). As an emulsion, the droplet assembly ages according to the classical ageing processes, such as flocculation, coalescence, gravitational separation, and Ostwald ripening [1]. In addition, molecular transport of solutes between the droplets – driven by differences in chemical potential of encapsulated molecules – is driving the system towards its equilibrium. This process is not really crucial for emulsions used in material science as all droplets are virtually identical in composition. Here such a transport process leads to cross-talk between droplet microreactors [24–27]: the concept of individual, independent microreactor ultimately breaks down at sufficiently large time-scale, compromizing the feasibility of assays based on the compartmentalization approach.

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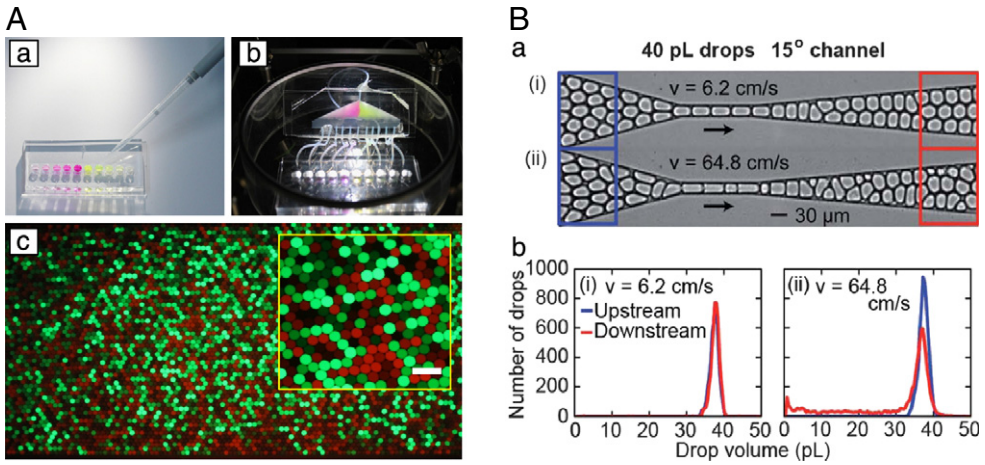

Fig. 1. Microfluidic manipulation of emulsions. (A) Complex emulsions are produced using microfluidics. Each droplet in the emulsion can have its own individual composition as shown here with fluoresent dyes (Reprinted with permission from Lim et al. [20] Copyright 2015, AIP Publishing LLC). (B) The manipulation of emulsions in microchannels leads to new types of ageing processes that need to be understood and controlled (Reproduced in part from Rosenfeld et al. [21] with permission of The Royal Society of Chemistry).

The understanding of mass transfer – and ageing processes in general – in these emulsions is essential for the establishment of platforms usable for biotechnological high-throughput applications. Reversing the viewpoint, the control of these transport processes between droplets can also open new ways to temporally programme the composition of droplet microreactors and design novel materials and microsystems.

2. Manipulation of emulsions in microfluidics

2.1. Droplets in microchannels

The most widely used channel geometries for microfluidic droplet production are the T-junction and the flow-focussing geometries – where the breakup of a stream of a first fluid is induced through shearing by a second fluid [6,28,10] – or step emulsification – where capillary forces at a step change in the height of a microchannel drives droplet formation [29]. In all cases, highly monodisperse droplets are formed due to the homogeneous shearing and the controlled emulsification conditions. Droplet production frequencies are ranging from a few to more than 10 kHz [30,31,20] with volumes down to the femtolitre range [31,32]. Several techniques have been developed to further manipulate, sort, split, trap or fuse droplets in microfluidic devices [10]. Besides their interest for applications [15], the tools for immobilizing, arranging and spacing droplets in a predefined way, allows significantly reducing the degree of freedom of an emulsion system and quantitatively address the dynamics of interfaces at small scales. Such tools appear especially interesting as a means to study physico-chemical processes in emulsions at the length-scale and time-scale of relevance. From a technology view-point, controlling the physico-chemical properties of the formulations used in microfluidics is essential to guarantee that droplet manipulation in channels is effective and reliable.

The manipulation processes in microfluidics are controlled by several dimensionless numbers. The viscosity ratio between both phases, the ratio of the droplet size to the channel dimension, and all the hydrodynamic dimensionless numbers control the droplet behaviour, in addition to all the dimensionless numbers defined to account for channels geometry. Among others, the capillary number $Ca = \eta U/\gamma$, where η is the viscosity (usually taken for the continuous phase), U the droplet velocity and γ the interfacial tension, has a crucial role. As an example, the capillary number controls the splitting of droplets at a constriction during flow (Fig. 1(B)) [21]. For a fixed processing speed (or throughput), reducing the capillary number is favourable to guarantee that interfacial effects dominate the physics of the system. Therefore η should be 'small' and γ 'large'. This condition determines what an efficient surfactant formulation should be for a reliable manipulation of the droplets: the continuous phase should have a viscosity as low as possible while the interfacial tension should be as high as possible. We will see below how formulations based on fluorinated oils match these requirements.

2.2. Understanding the dynamics of surfactants at interfaces

The surfactant plays a key role in the stabilisation of the interfaces. The dynamics of the droplet deformations will be determined by the properties of the surfactant. Classically, surfactant adsorption is measured using tensiometry on large volumes. It was, however, shown that the dynamics of adsorption of surfactant is essentially different at 'large' scales compared to 'small' scales [33]. Here, large and small are defined by a discussion on the two limiting cases for adsorption: the adsorption is either limited by the bulk diffusion of the surfactant to the interface (diffusion-limited adsorption) or by the reaction rate of adsorption of molecules to interface (kinetic-limited adsorption). The crossover between both regimes occurs for a droplet size $R^* = D/k_{ads}\Gamma_\infty$ where D is the diffusion constant, k_{ads} the forward rate of adsorption and Γ_∞ the maximum interfacial concentration of the surfactant. Typically, R^* is of order 10–100 μm [33]: At small scales, adsorption/desorption controls the dynamics of surfactant. Tensiometry on large volumes (even using pendant droplets with volumes of ~1 μL) is diffusion limited and does not provide the relevant information to understand the surfactant dynamics at the scale of emulsion droplets. Over the past years, microfluidic systems have been designed to address the questions dealing with interfacial tensiometry at the relevant scales [34,35] with a recent focus on the dynamics of surfactant-laden interfaces [36–38]. In this context, a full understanding of droplet flow in the presence of surfactant is far from being reached. Open-questions involve the dynamics of interfaces in confinement and the role of Marangoni stresses and interfacial rheology on the behaviour of droplets in confinement.

3. Mass transport in emulsions

The second class of problems related to ageing deals with the transport of compounds between the droplets. Mass transfer between emulsion droplets occurs as a result of phase partitioning due to a finite