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# Transient behavior and relaxation of microcapsules with a cross-linked human serum albumin membrane

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ABSTRACT

Capsules consist of droplets enclosed by a membrane with shear resistant properties especially when fabricated by interfacial cross-linking. In many applications, the protection and release of the internal medium need to be strictly controlled. It is possible to tune the membrane mechanical properties by changing the physico-chemical conditions of the fabrication process, but a good control of the production requires their characterization, which is a scientific challenge, since the objects are a few tens of microns in size at most. One advantageous approach is to resort to microfluidic techniques. We study the transient response of capsules having a cross-linked human serum albumin (HSA) membrane, as they flow through a sudden expansion. We determine the characteristic time scales of the capsule relaxation and compare them to the ones predicted by a full numerical model of the relaxation of a capsule flowing in a rectangular channel, for which the membrane is assumed to be purely elastic. We show that the membrane is viscoelastic and that the relaxation is solely a function of the ratio of the relaxation time to the convective time.

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## 1. Introduction

Capsules, which are liquid droplets enclosed by a thin elastic membrane, are widely found in nature (red blood cells, fish eggs). Among all their industrial and clinical applications, one can highlight their extensive use in cosmetics and the great potential they offer in bioengineering and in medicine: by encapsulating drugs, genetic material or cells, capsules have found applications in targeted drug delivery and in the development of bioartificial organs and biosensors (Orive et al., 2004; Lam and Gambari, 2014). The deformable membrane that separates the internal and external liquids controls the potential diffusion and degradation of the internal substance, as well as its rate of release when it occurs.

Artificial capsules can be obtained through gelation or interfacial polymerization of a liquid droplet. The current fabrication processes tend to lead to approximately spherical particles enclosed by a thin membrane with mechanical properties that depend on the fabrication procedure. The membranes can be made of natural constituents such as alginate, poly-L-lysine and proteins (Kühtreiber et al., 1999; Edwards-Lévy, 2011), or of synthetic polymers such as polyamid and polysiloxane (Walter et al., 2000; Koleva and Rehage, 2012). Poly-L-lysine and alginate membranes rely on electrostatic interactions between negatively and

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positively charged ions and consist of a gel. Protein and synthetic polymeric membranes are in contrast produced through interfacial cross-linking, which generates covalent bonds across molecules. The resulting membranes thus differ in mechanical properties. Cross-linked membranes have been shown to be more resistant to external constraints (Kühtreiber et al., 1999).

The motion and deformation of flowing capsules depend on the mechanical properties of the membrane. The behavior of artificial spherical capsules with a cross-linked membrane has been observed under steady simple shear flow (Walter et al., 2000; Koleva and Rehage, 2012; Chang and Olbricht, 1993; Rehage et al., 2002) and planar hyperbolic flow (Chang and Olbricht, 1993; Barthès-Biesel, 1991; de Loubens et al., 2014). Experimental studies show that the capsule takes in both cases an approximately ellipsoidal shape, which depends on the ratio between the flow strength and the membrane elastic resistance to deformation. The difference is that, in simple shear flow, the flow vorticity leads to membrane rotation around the steady capsule deformed shape.

The influence of confinement has been studied more recently by flowing millimetric or micrometric size capsules through cylindrical tubes (Risso et al., 2006; Lefebvre et al., 2008; Chu et al., 2011) or through square section microfluidic pores (Leclerc et al., 2012; Hu et al., 2013). In all the cases, the particle is deformed by the flow and reaches a steady-state shape, for which the membrane (and thus the inner fluid) is immobile within the reference frame of the flowing capsule. The capsule then takes the form of a slug or has a parachute shape at the rear depending on the confinement, flow strength and capsule rigidity.

One practical application of experiments of flowing capsules is to measure the mechanical properties of the membrane. Their identification requires comparing the experimental steady-state results with a suitable fluid–structure interaction model that simulates the same conditions as those prevailing in the experiment. The shear flow experiments can be analyzed with the asymptotic model of Barthès-Biesel and Rallison (1981), when the deformation is small to moderate. The pore flow experiments are analyzed by means of a full numerical model of the set–up, where the capsule membrane is assumed to have purely hyperelastic properties (Lefebvre et al., 2008; Hu et al., 2012). Since the membrane is motionless at equilibrium, the model is also appropriate to represent the equilibrium deformation of a capsule with a viscoelastic membrane. It has been shown that such models allow to correlate the membrane mechanical properties of cross-linked ovalbumin membranes to the physicochemical conditions of the capsule fabrication and thus to the cross-linking degree (Chu et al., 2011).

Thanks to the rapidly growing microfluidic technologies it is possible to design devices that are more complex than a straight uniform pore. Owing to fabrication constraints, the tubes usually have a square or rectangular cross-section. The objective of the paper is to investigate the feasibility of using a microfluidic channel with a sudden expansion to study the relaxation of a population of capsules subjected to varying flow conditions in order to detect whether there is any membrane viscosity. Very few experimental studies have investigated the membrane viscosity of artificial capsules. Chang and Olbricht (1993) considered 2 to 4-mm size capsules with nylon membranes and followed their transient shape and orientation under Couette flow. They obtained an estimate of the membrane viscosity and elastic Young modulus from a comparison of the experimental deformation to the one predicted by the small-deformation theoretical model of Barthès-Biesel and Sgaier (1985). A larger number of experimental techniques have, however, been developed in the 1970s and 1980s to determine the membrane viscosity of red blood cells. They involve quite complex experimental setups based on the time-dependent recovery after the removal of micropipette aspiration (Chien et al., 1978) or of an elongating traction force (Hochmuth et al., 1979), or else on the measurement of the tank-treading frequency (Tran-Son-Tay et al., 1984). Recently, Tomaiuolo et al. (2011) have measured the transient deformation of red blood cells flowing in a microfluidic diverging channel. Using a Kelvin–Voigt model for the global deformation of the cells, they obtained an estimate of the membrane viscosity.

In the present study, the transient behavior of artificial capsules with a diameter of the order of 120 μm will be investigated in a microfluidic channel composed of a square section tube followed by a co-axial rectangular one. The experimental results will be compared to a numerical simulation of the relaxation of a capsule from a square channel to a rectangular one in the case of a purely hyperelastic capsule membrane. The capsule will be released into the rectangular channel with the deformed shape that it takes at steady state in the square channel. By comparing the characteristic times of relaxation obtained in the numerical and experimental cases, we will be able to determine whether the capsule membrane is viscoelastic or purely elastic.

## 2. Materials and methods

### 2.1. *Preparation of capsules suspensions*

Capsules are prepared from an emulsion of droplets of aqueous buffered human serum albumin (HSA) solutions (pH 8) suspended in cyclohexane, in which are added a surfactant (sorbitan trioleate) and the cross-linking agent (terephthaloyl chloride). Two mass concentrations of HSA are considered: [HSA]=20% and 30% (weight/volume), which correspond to 20 or 30 g of solute dissolved in 100 mL of the aqueous solution (these concentration units are the ones that are classically used in chemistry and biology). In the following, the two capsule populations will be denoted HSA20 and HSA30. The reaction time is 30 min and the stirring speed is 1700 rpm. The diameters of the investigated capsules lie in the range 110–124 μm, with an average value of 119 μm. After fabrication, the capsules are rinsed successively in an aqueous solution of polysorbate, and thrice in pure water. They are then transferred into glycerol for storage.

### 2.2. *Microchannel*

The microchannel is fabricated by molding liquid polydimethylsiloxane (PDMS) onto a silicon master mould, baking it and peeling it off. The PDMS replica is then bonded onto a glass lamella by air plasma (Plasma cleaner, Harrick). The channel

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