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Microfluidic separation processes using the thermodiffusion effect

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ABSTRACT

The numerical and experimental results presented in this work show that a relatively small temperature gradient (5K), has great potential to generate a separation in interesting mixtures for biological purpose. In fact, it improves molecular diffusion separation process of a protective cryo (10% of dimethyl sulfoxide (DMSO) in phosphate buffered saline (PBS)) for cryopreserved cells, by 10%. This separation process was analyzed both numerically and experimentally, for which it was necessary to determine experimentally the thermophysical and transport properties of the mixture of 10% of DMSO in PBS. Experimental tests were done in a microdevice with a working section of 500 μm × 25 mm and a length of 75 mm, which was designed, constructed and first of all validated with the mixture of reference H2O-Isopropanol at a mass fraction of 50%. Experimental test with the protective cryo were done with inflow rates between 1000 μL min and 4000 μL/min. The results confirm that the effect of thermodiffusion must be considered in handling processes of biological fluid mixtures because the existence of a thermal gradient could improve the efficiency of the separation process in microdevices.

1. Introduction

For more than two decades, it has been considered that the miniaturization of test systems and procedures provide great advantage in diverse industries, particularly in the biotechnology sector [1]. This miniaturization requires the development of microfluidic platforms using a variety of devices in sample preparation, detection and diagnosis, mainly centered on the health sector. Many of these devices need efficient mixing and separation procedures, applied to molecules, analytes or particles [2]. As a result, in recent years, there have been countless numbers of new techniques and procedures developed for this determination [3,4]. These techniques can be separated into two categories: i) passive devices, in which the separation or mixing operation is removed without the application of any external force, ii) active devices where actuators or external forces are employed for this goal.

Submillimeter dimensions of the channels used in microdevices, affects negatively in the operation of mixing or separation, because flows are purely laminar [5]. The absence of convection leads to do the mixing process under a purely diffusive regime. In order to optimize the mixing process in the majority of microdevices, T or Y geometries are used as references [6] [7] [8]. Similarly, chaotic advection has been used, which is based on breaking the laminar flow of sharp changes in geometry [9], or by introducing obstacles in the main channel in the form of poles [10] or grooves [11]. The possibility of improving the process of mixing, forcing a transverse vortex called “Dean Flow” which introduces curvature in the main channel also has been studied [12], or applying acoustic fields [13], electric fields [14], magnetic fields [15] and others [16] [17].

Detection, quantification and analysis of clinical samples such as DNA, proteins or amino acids, require efficient separation processes, and several studies have attempted to develop such microtechnology [18] [19]. Passive separation devices are used in applications involving the preparation of biological samples such as separation of blood plasma by capillary action [20], sedimentation [21] or the Zweifach-Fung effect [22]. For the extraction of different size analytes, filters were developed with H shape, where analytes are extracted due to the molecular diffusion coefficient difference [23]. Hydrodynamic forces have also been used for the separation of particles to control the entry conditions in curved channels [24], and straight channels [25]. The development of active microseparators has employed centrifugal [26], ultrasonic [27], electrical [28] or magnetic fields [29]. The implementation of such devices increases efficiency, however, technical complexity makes it more difficult to integrate them into microfluidic platforms. This is why so many advances have been made in passive separation, although it is inefficient and very complex [30].

Active devices, even if they are for mixing or separation, are more effective than passives. However it is more complicated to embed those devices in microdevices as well as their control. For this reason there has been much research conducted in the development of passive devices to increase the efficiency up to the active ones in mixing and separation processes [30].

One of the applications of microfluidic devices is cleaning

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cryopreserved cells, which involves removing the protective cryo by molecular diffusion [31] [32]. Such these protective cryo is dimethyl sulfoxide (DMSO), which is mixed with PBS (phosphate buffered saline), used to cryogenate cells, tissues or organs [33]. Although DMSO protects the cell from freezing, exposure for a prolonged period has adverse impact on the cells [34] [35]. Therefore, cleaning is necessary before clinical application. The standard technique is the spin cleaning, however, this process may damage up to 30% of the cells [36]. This makes microdevices an attractive alternative.

Nevertheless, microdevices utilized for extracting DMSO from cells may have limited applicability because separation by molecular diffusion may be excessively slow. This study offers an experimental and numerical study in microdevices in order to optimize the separation efficiency of biological fluids using thermodiffusion effect by applying temperature gradients [37].

Thermodiffusion in liquids has been extensively examined [38], since it was discovered that a temperature gradient generates a redistribution of species in a mixture [39]. Later and independently, Soret quantified this in greater depth [40]; this is why the phenomenon of thermal diffusion is also known as Ludwing-Soret effect. The Ludwing-soret effect was an important development as it enabled the analysis of the partial separation of components in a mixture by the application of a temperature gradient. This phenomenon has great importance in many natural processes, such as in the dispersion of components of oil wells [41] [42], or the dispersion of the components in the magma [43], in the characterization of isotopes [44], even in the distribution of elements in creating life [45] and also in biological fluids such as DNA, proteins or bacteria [46] [47] [48].

The result of applying a temperature gradient to a binary mixture generates a species flow according to Equation (1):

$$\vec{J} = -\rho D \nabla c - \rho D_T c_0 (1 - c_0) \nabla T \quad (1)$$

Where D is the molecular diffusion coefficient, c is the mass fraction of the component of interest and c_0 is the mass fraction of this component at the reference state, ρ is the density, D_T is the thermodiffusion coefficient and ∇T is the temperature gradient applied. The second term of Equation (1) quantifies the flow separation created by the temperature gradient within a mixture, which is governed by the thermodiffusion coefficient. The first term, quantifies the mixture flow caused by concentration gradient, which is dominated by the molecular diffusion coefficient. When the denser component is led to the cold wall is called positive Soret effect, and the opposite is called negative Soret effect. Therefore, in order to understand the behavior of a mixture under the temperature gradient it is essential to quantify the value and the sign of the Soret coefficient. This is because the magnitude and sign can vary for the same mixture as a function of the concentration [49], average temperature [50], or even colloidal size [51].

2. Determination of thermophysical and transport properties for DMSO/PBS mixture with a mass fraction of 10% of DMSO

2.1. Thermodiffusion coefficient

To determine the mass flow generated within a mixture under the temperature gradient it is essential to know D_T and D. In order to determine experimentally D_T the Thermogravitational column technique in a flat configuration has been used (Fig. 1).

The mixture is confined inside the gap and subjected to a horizontal temperature gradient. This temperature gradient is achieved by two tempered recirculating baths at $T_0 + \Delta T/2$ and $T_0 - \Delta T/2$ in each wall. The temperature gradient causes a horizontal separation of the mixture components inside the thermogravitational column (CT). The gravitational field effect enforced convection, thus generating a vertical separation. The Thermodiffusion coefficient can be determined once the solution reaches steady state using the FJO theory from the segregation

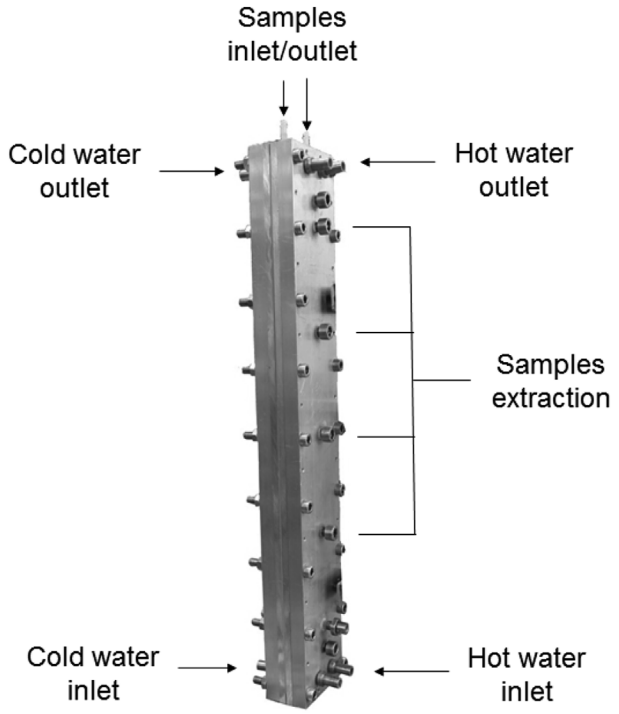

Fig. 1. Thermogravitational column (dimensions of the inner gap: 1 mm × 50 mm x 500 mm).

by equation (2) [52] [53].

$$D_T = -\frac{g L_x^4}{504} \frac{\alpha}{c_0(1 - c_0)\beta\mu} \frac{\partial \rho}{\partial z} \quad (2)$$

Where μ is the dynamic viscosity, L_x is the inner gap of the CT, $\alpha = -(1/\rho)(\partial\rho/\partial T)$ is the thermal expansion coefficient, $\beta = (1/\rho)(\partial\rho/\partial c)$ is the mass expansion coefficient and g is the gravitational acceleration.

In this experiment the density gradient $\partial\rho/\partial z$ was obtained by measuring the density of the extracted samples (4 in total) at different heights in the column, once the steady state was reached (Fig. 2).

In order to obtain the mass expansion, a calibration of the density in function of the concentration was carried out. To achieve this, several samples with concentrations ranging for higher and lower to the average were tested at a temperature of 25 °C, (Fig. 3a). Similarly, the thermal expansion coefficient was determined measuring the density of the mixture in function of the temperature (Fig. 3b). To determine these coefficients, the density was obtained by an Anton Paar densitometer DMA 5000 vibrating U quartz tube with a resolution of 1.10^{-6} g/cm^3, and with temperature control based on a Peltier system with a

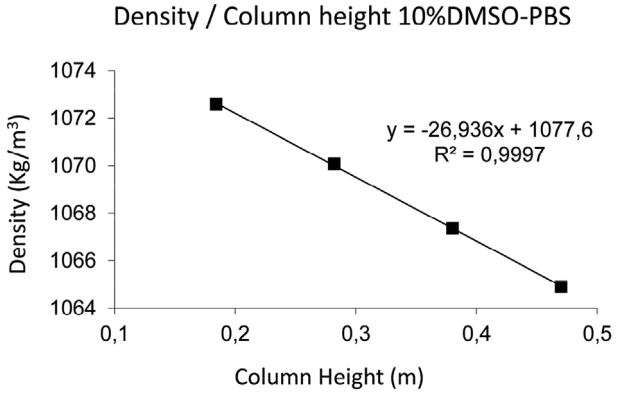

Fig. 2. Density in function of the height of the TC in the steady state, for a mixture of DMSO/PBS to a mass fraction of 10% DMSO at 25 °C.