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Measurement of Diffusion in Flowing Complex Fluids

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Abstract

A microfluidic device for the measurement of solute diffusion as well as particle diffusion and migration in flowing complex fluids is described. The device is particularly suited to obtaining diffusivities in such fluids, which require a desired flow state to be maintained during measurement. A method based on the Loschmidt diffusion theory and short times of exposure is presented to allow calculation of diffusivities from concentration differences in the flow streams leaving the cell.

Keywords

microfluidic; diffusion; migration; complex fluid; diffusivity

Introduction

We describe a microfluidic device for the measurement of solute and particle diffusion coefficients in flowing complex fluids. We report here the theory and design of the device and preliminary measurements of the well-established diffusion coefficient of albumin in aqueous media, made in order to validate both the adherence of the apparatus to the flow patterns predicted for it and the analytical model used with it to estimate diffusion coefficients.

By definition, complex fluids contain a dispersed phase whose elements are of supramolecular scale. These elements generally exhibit an average motion that is different from the average motion of the surrounding continuous fluid phase to a degree that is largely determined by the forces applied to the system. In many instances, fluid motion also changes the spatial distribution and the direction and rate of rotation of the dispersed elements in a manner that also changes the microscopic and macroscopic motion of the continuous phase [1]. It is thus necessary to study migration of elements of the dispersed phase and dispersion of components of either phase under the conditions of fluid movement that are of interest. The problem is of wide concern, occurring in emulsions, colloidal solutions, suspensions of micro- and nanoparticles and gas-liquid mixtures. It has, however, nowhere been of more concentrated concern than in attempts to understand solute and cell movement in blood.

The study of dispersion in flowing complex fluids has required the imposition and measurement of a gradient, either of an entity of interest, or at least a tracer-labeled part of that entity. Two principal methods of imposing a gradient have been employed: release or capture of entity at a boundary of the flow, Taylor dispersion [2-4], or juxtaposition of two streams with different entity concentrations [5,6]. (In complex fluids, selective photoactivation is not often a suitable means of establishing a known diffusion gradient because such fluids have complicating optical properties.) When the entity can be supplied by generation or infiltration from, or capture by, a wall, and when a transverse distribution of the entity can be obtained downstream of the point of introduction, it is possible to assess the diffusional characteristics of the medium, although usually through a model that requires knowledge of both the reactive and diffusional behavior

of the entity. As shown by Taylor and as subsequently modified by Aris and others [7], a sharp change in entity concentration can be made at the entrance of a suitably long flow path, and if the velocity distribution in the flowing fluid is well known, diffusional behavior can be inferred from the time dependent concentration of the entity exiting the path.

Colton et al. [6] measured diffusion coefficients of urea in flowing blood. Their use of a membrane to create a gradient required use of a measured membrane permeability. This additional variable (effectively, the membrane serving as an added resistance to transfer) increases the complexity of their model and adds some uncertainty to the result.

In the 1980's, Giddings [8-10] and his students showed that two miscible fluids could be made to flow side-by-side, with diffusional exchange between them that was measurable by careful splitting of the combined streams, followed by determination of concentration changes in either or both streams. Their work addressed important aspects of the problem considered here: the migration of elements of a dispersed phase responding either to an externally applied transverse force field (*e.g.* gravity) or to forces derived from the fluid motion itself. They also addressed, in homogeneous liquids, the measurement of diffusion as well as migration caused by external forces (*e.g.* magnetic or electrical forces). Diffusion among elements of the dispersed phase and the influence of dispersed phase movement on diffusion within the continuous phases appears not to have been addressed.

Experimental System

Absent a microfluidic geometry, the amount of exchange relative to the axial flow of a solute is generally very small. We have devised a microfluidic flow path that allows the combination and subsequent separation of two fluids arranged in either two or three layers. The flow of the two fluids together is laminar over a wide range of shear rates, and exchange between the fluids is diffusional, sufficient to induce easily analyzed changes in concentrations between entrance and exit within each of the fluids. We report here the construction of the apparatus, techniques for using it, and a simple model for estimating diffusion coefficients from the concentration changes it induces. We also report corroborative simulations of the flow pattern within it, and the successful measurement of the well established diffusion coefficient of bovine serum albumin in aqueous solution.

Apparatus construction

Microfluidic flow paths have been constructed with cross-sections that are rectangles with large aspect ratios. The narrow dimensions of these rectangles are as small as 75 micrometers and may be wider than 2 cm, resulting in slits with aspect ratios that can be greater than 200:1. The slits are cut through metal bars (billets), generally made of stainless steel (see Figure 1). The slits are cut by wire-EDM, using a Mitsubishi Model RA90 electrical discharge machine. (Wire-EDM is a commercial process that draws a thin, electrically charged wire through a slab of conducting material, as the material is moved perpendicular to the wire. Electrical discharge between the wire and the slab forms an erosion plane in the metal, parallel to the axis of the moving wire.) The devices whose performance is reported here were fabricated using brass wires with diameters of 0.006 and 0.010 inch. Cover plates were machined from methyl-methacrylate polymer with a thin gasket interposed between the plates and the billet. The assembled apparatus is shown in Figure 2.

Fluid enters and leaves the slits through holes drilled in the billet. Six holes are shown in Figure 1. These holes connect to connectors mounted on the methacrylate cover plates. The slits allow the combination of two or three fluid streams within the billet and can be arranged in different patterns to minimize advective mixing at points of entry and separation. A slit length before mixing may allow migration of components in one or more of the fluids before they contact

each other (Figure 3). When two side streams are used, they are usually from the same source, and together they sheath a center stream that comes from a separate source. The flow streams are separated at the end of the common slit and are drawn out of the apparatus through slits that are usually mirror images of those used to introduce the fluids. Whenever two streams are in direct contact, they must flow in the same direction, as shown.

Experimental procedure

Bubbles were removed from the apparatus by flushing the volume first with gaseous carbon dioxide, then with dilute sodium hydroxide in deaerated water, then copiously with pure deaerated water. All feed solutions were filtered through stainless-steel screens with 80 micrometer openings and were delivered to the billet by syringe pumps driven by digital stepper motors. In these experiments, $n-1$ ($n = 4$ or 6) pumps were used to control all but the inlet flow of the center stream, which was drawn from a small, magnetically stirred, open volume. Samples of the effluent streams were taken and analyzed after a waiting time greater than 10 times the residence time of the flowpath and after any measurable trend in exit concentration had disappeared.

When the apparatus is fed with two streams, the interface is located near the center-plane of the slit, and the interfacial shear rate will be zero. When a center stream is sheathed by two side streams of equal composition and flowrate, two symmetric interfaces are formed each between the center-plane and one of the two walls, and their shear rates are equal and finite. (When the combined sheath flows equal that of the center flow, the interfaces for the Newtonian fluids considered here occur at approximately $1/3$ (more accurately 0.3417) of the distance from the centerline to either wall.)

Data Analysis

All data were taken under conditions that limited the effective diffusion distance to a fraction of the film thickness, and all data have been analyzed assuming the fluid velocity at the interface (s) to be known and the effect of shear-related velocity variations in the thin, adjacent fluid layers to be negligible. Given these assumptions, exchange across each interface is comparable to what takes place at the mid-plane of a Loschmidt apparatus [11]. There, two fluids of different concentration are placed in contiguous containers of height B , and are suddenly exposed to each other through a contact area A , for a time τ . The contact area is then masked and each fluid is subsequently analyzed. In the present case, transfer between two flowing streams each of thickness B can be envisioned similarly, using the length of the combined flow path, L , and the interfacial velocity v to estimate the exposure time, τ , as L/v (Figure 4). If a center stream of thickness B is sheathed by two similar streams, each of thickness $B/2$, the system can be considered as divided at the center of the slit into two independent systems each with two layers of thicknesses $B/2$, exposed to each other for a time τ equal to L/v . If the quantity

$\frac{\mathcal{D}\tau}{B^2} < 0.4$, the quantity of material transferred is independent of the stream thicknesses B and is equal to $w = c_0 L W \sqrt{\frac{\mathcal{D}\tau}{\pi}}$, where the diffusion coefficient is represented by $\mathcal{D}$, the width of the flowing stream by W and the concentration of the solute-rich stream by c_0 . This equation is the classical solution of the equation for unsteady diffusion into a semiinfinite slab [12]. During the time interval τ , the quantity of solute fed to the transport region is equal to $q_c c_0$, where q_c is the flowrate of the solute-rich stream and the quantity of solute removed by the receiving stream (s) is $q_s \bar{c}$. If the solute-rich flow q_c and the aggregate receiving stream flow q_s are equal the

extraction ratio $E = \frac{\bar{c}}{c_0}$ can be calculated and used to estimate the diffusivity: $\mathcal{D} = \tau \left(\frac{q_c E}{0.5642 n L W} \right)^2$, where n equals either 1 or 2 as there is respectively one interface (two streams) or two interfaces (three streams).

The principal error in the application of this analysis to a flowing system is its failure to recognize that the residence time of all fluid layers is not identical. This error is expected to be least with two streams of equal flow; then the interface is at the center of the combined flow (where the shear rate is zero).

Preliminary Measurements

For the experiments reported here Bovine Serum Albumin, Cohn fraction of 5 (Equitech-Bio Inc., Kerrville, Texas) was dissolved (5 wt %) in isotonic saline. Experiments were conducted at room temperature, $\sim 21^{\circ}\text{C}$. A portion of the albumin solution was dyed with Evans Blue (Sigma-Aldrich E2129), 3 moles dye/mole albumin. This solution was fed into the central feed slit. Electrophoresis and dialysis failed to reveal any free dye in the dyed albumin. The fraction of dyed albumin in the sheath streams was determined spectrophotometrically and was compared to the center stream feed after dilution by a known amount to approximate the dilution observed in the exit sheath stream. Two billets, each with a length of the diffusion path, L of 7.32 cm and width 1.22 cm were fed at equal flowrates such that the interface region Reynolds number is ~ 5 (assuming a solution viscosity of 1.2cP). One billet was operated in the manner of figure 3-a above, or 3-layered, with the feed channel heights being 300 μm each. The second billet was operated in the manner of figure 3-d above, or 2-layered, with the feed channel heights being 190 μm each. The reported diffusion coefficient for each set of experiments is $6.35 \cdot 10^{-7} \text{ cm}^2/\text{s}$ [13, 14]. The measured diffusion coefficients for the two experiments were both $7.6 \cdot 10^{-7} \text{ cm}^2/\text{s}$ each, or 1.2 times the previously reported value (Table 1).

Summary

The device described here allows measurement of diffusion and migration of complex fluid components during laminar microfluidic flow. A simple fabrication method is described that allows channels of small height, high aspect ratio and arbitrary length to be constructed in ordinary materials, *e.g.* stainless steel, and for streams to be fed, combined into a principal channel, and subsequently separated. External adjustment of flows, as well as variations in design of the apparatus, allows the combined fluid stream to be composed of different amounts of two or more feed streams. Variation, thus, of the location of the interface between the two streams that comprise the combined stream, coupled with short exposure time of each stream to the other, allows controlled exploration of diffusion in different parts of the combined stream. For the data reported here, there should be no effect of shear on diffusivity. Thus, the coincidence of the two- and three-stream values is encouraging in light of the approximate theory used to extract the diffusivity from the measurements. In complex fluids diffusion can be expected to be shear sensitive and it would be hard to identify by other means, given the complicated velocity and component distributions during flow of complex fluids.

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Figure 1. Stainless steel billet faced on front and rear by acrylic plates through which feed and exit streams pass.

Figure 2.

Assembled system. The stainless steel billet is sandwiched between acrylic plates that have appropriate attachments to allow for tubing connections controlling the flow into the cell. The top acrylic plate has a cut-out window to allow for viewing the edge of the flow path with a microscope.

Figure 3.

Different slit patterns formed with wire-EDM in the stainless steel billet. Flow is from left to right, and enters and exits via tubing connectors that are indicated by circles. Patterns (a), (b), and (c) accommodate three-stream flows, (two separate interfaces) whereas pattern (d) accommodates two-stream flows (single interface). Patterns (a), (b), and (d) have symmetric entries. Pattern (c) has a staggered, asymmetric entry. Pattern (b) provides a short exposure time.

Figure 4. Schematic view of flowing-stream analog to the Loschmidt analysis. Each of the 2 layers is of height B , and the transfer of an entity from one phase to the other induces a symmetric concentration gradient.

Table 1

Apparent (measured) diffusion coefficients of bovine serum albumin in saline for 2 independent systems, and their ratios to theoretical diffusion coefficients.

System Description	$D_{\text{Apparent}} (\times 10^7 \text{ cm}^2/\text{s})$	$D_{\text{Ratio}} (D_{\text{Apparent}}/D_{\text{Literature}})$
3-Layer, 300 μm feed channel heights	7.64 ± 1.6	1.2
2-Layer, 190 μm feed channel heights	7.61 ± 1.2	1.2