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COMMUNICATION

Steric Field-Flow Fractionation: A New Method for Separating 1 to 100 μm Particles

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Abstract

Steric field-flow fractionation (steric FFF) is described as a high field limit of normal FFF that separates particles according to their diameter or radius. Retention equations are used to describe the phenomenon; these equations lead to the suggestion that steric FFF is applicable to particles from 1 to 100 μm as a minimum range. Conditions that control resolution are discussed, and fundamental similarities and differences between steric FFF on one hand and normal FFF and hydrodynamic chromatography on the other hand are noted. Optimum flow conditions are discussed and the complication of describing the migration of irregular particles is noted. Preliminary experiments with glass beads of ~10 to 30 μm diameter demonstrate the existence of fractionation.

The separation of particles having diameters in the general range 1 to 100 μm has considerable technological importance in biology, industry, and environmental control. While various sedimentation and filtration methods have been applied to distributions of such particles, speed and resolution often leave something to be desired. We propose here a method which may complement existing techniques in this size range.

This new method is an extension of field-flow fractionation (FFF), which normally works best with micron and submicron size particles. Because of the common origin, we categorize the new technique as an FFF method and give it the specific name, steric field-flow fractionation, or

steric FFF. Although steric FFF bears a relationship both to the parent FFF technology and to hydrodynamic chromatography (HC), it has certain theoretical advantages possessed neither by normal FFF nor HC.

FFF as a general technique utilizes a field applied perpendicularly to a flow channel in such a way that particles of different size are forced into equilibrium layers of different effective thickness against one channel wall (*1*, *2*). The mean thickness, *l*, is determined by the interplay of field-induced forces which tend to compact the layers and Brownian motion which tends to disperse them. Usually the largest particles form the most highly compressed layers. Consequently, with the initiation of flow in the channel, the largest particles are found in the slow flow regions near the wall, and their migration downstream is therefore retarded relative to the migration of smaller particles. Because of this differential migration, particles of different size emerge from the channel at different times, and can be detected or collected as distinct fractions.

Steric FFF is the high field limit of normal FFF. As the field strength in an FFF system is increased, particles are pushed with increasing firmness against the wall. Steric FFF is realized when the mean Brownian displacement from the wall, *l*, becomes less than the particle radius, *a*. In this domain, particles extend out into the flow stream primarily because of their own finite size. In this case differences in *a* rather than differences in *l* will be responsible for differential migration. The term "steric FFF" is used to indicate that layer thickness is now controlled by the steric exclusion of particles from space occupied by the wall.

The principles of steric FFF are illustrated in Fig. 1. Clearly, in this system, large particles migrate in advance of small particles and emerge

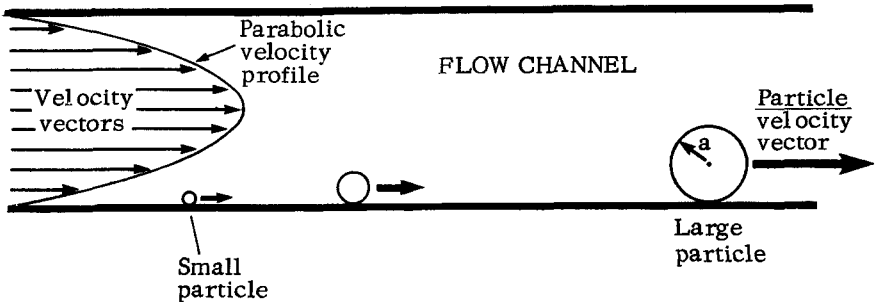

FIG. 1. Schematic diagram of the side view of a steric FFF channel, showing the relative difference in velocity vectors that will control the migration of particles of different radii.

from the channel first. This is an inversion of the normal elution order of FFF systems.

The existence of a fractionating effect when $a > l$ was established theoretically in an earlier publication from this laboratory (*3*). In that paper the retention ratio R (channel volume/particle retention volume) was given approximately by the limiting expression

$$R = \frac{6a}{w} + \frac{6l}{w} \tag{1}$$

The second of the two terms controls selectivity and separation in normal FFF. The first of the two terms dominates the selectivity in separations achieved by steric FFF. This requires, as mentioned previously, that l be made small by increasing the field to high levels.

We note that Brownian displacement l nearly always decreases as radius a increases. Therefore changes in the two terms in Eq. (1) with a change in a tend to cancel one another so that the two effects cannot be beneficially combined. One should use one or the other as a dominating influence. The present proposal requires that the first term in Eq. (1) be the dominant factor. In this case Eq. (1) can be written approximately as

$$R = 6a/w \tag{2}$$

Retention volume $V_r = V^0/R$ is therefore given by the expression

$$(V_r/V^0) = w/6a \tag{3}$$

which shows that V_r is inversely proportional to particle radius a. The strong dependence on a provides the selectivity necessary for realization of the method.

We recognize that the above equations are approximate. They are based on the usual assumption of FFF theory that particles will migrate at the unperturbed stream velocity at their center of gravity. However, in steric FFF, particles will virtually roll or tumble their way downstream along the wall. Energy dissipation due to the rotational motion will tend to reduce the translational velocity relative to the values predicted by Eqs. (2) and (3). Nonetheless, the latter equations still serve as a rough guide for the potential scope of steric FFF.

The practical particle size range of steric FFF will be largely fixed by the w/a ratio in Eq. (3). The method will probably function best with $20 > V_r/V^0 > 2$, although the upper limit, particularly, might be very expandable. The range corresponds to $120 > w/a > 12$ from Eq. (3), or, approximately, to $100 > w/a > 10$. At present it is difficult to construct

uniform channels less than 50 μm thick. Therefore $a = 0.5$ μm (diameter = 1 μm) is a tentative lower limit for good performance. By contrast, a 500 μm (0.5 mm) channel will yield an upper limit of 50 μm radius particles (100 μm diameter). Thicker channels would undoubtedly extend this limit if desired. Therefore, a very conservative working range is one that includes particles between 1 and 100 μm in diameter.

In theory, any kind of external field (electrical, sedimentation, etc.) can be utilized for steric FFF, just as for normal FFF. However, gravity provides a practical field for most particles in the 1 to 100 μm diameter range unless they are in a neutrally buoyant medium.

We note that for some particles and some surfaces there will be a tendency for adhesion and for trapping in small surface cracks and indentations. To combat this, surfaces that are inert and flat should be employed. Furthermore, we suggest that the flow velocity should be sufficiently high that the viscous forces dragging and rolling the particle along should exceed the gravitational forces pulling the particle against the surface. In this way the particle would tend to be pulled immediately free of any ensnaring influence. Therefore high flow velocities appear to be advantageous for steric FFF separations.

By contrast, high flow velocities hinder resolving power in normal FFF. In FFF and HC, particles undergo Brownian (or hydrodynamically forced) excursions over a wide range of stream velocities. Separation relies on differences in average velocities, but velocity fluctuations interfere with separation and must be subdued. In normal FFF, and to a lesser extent in HC, velocity fluctuations are reduced by decreases in flow. However, in steric FFF, the Brownian excursion distance is negligible, and such fluctuations are not important. Spherical particles should migrate at a remarkably uniform velocity in such a system.

Particles of irregular shape present a more complicated picture. A tumbling motion is expected. One could imagine a particle dancing up and down as it tumbled randomly over its different extrema. However, if flow velocities are high and flow forces exceed gravitational forces, as suggested earlier, the particle may not have time to "settle" between individual tumbles, and it, too, may be carried along at a fairly constant velocity and at a height just skimming the surface. In this case radius a, defining migration velocity in Eqs. (2) and (3), would tend to be that along the longest axis of the particle.

The mechanics of the motion of irregular particles in steric FFF is centrally important and requires much more investigation. Separations can

undoubtedly be obtained without such studies, but if the full potential of the method in characterizing particle sizes and particle size distributions is to be realized the major features of this motion must be understood.

While steric FFF is a natural extension of FFF technology, it is also related to HC, as noted earlier. HC normally operates in a column packed with fine beads. Separation occurs in the interstitial space between the beads (*4*, *5*). HC, like steric FFF, works on the principle of steric exclusion: particles are excluded by their own finite size from hugging fixed walls, and they are therefore forced toward the center of the adjacent flow stream. However, within those steric limits, they can occupy any part of the interstitial flow stream. This freedom increases velocity fluctuations, as noted earlier. More importantly, it reduces selectivity by allowing particles of different sizes to intermingle in the space they occupy and therefore to overlap in the local velocities with which they are carried downstream. No selectivity can be generated in a common volume occupied without restraint by different particles. Unfortunately, the common volume, even for particles at the practical size extremes, is 80 to 90% of the total void volume in the HC column.

Steric FFF differs fundamentally from HC, then, by utilizing an external field to compress each particle size into a unique layer whose position is defined by steric limits. The applied force minimizes both fluctuations and overlap. Hence band broadening should be small and selectivity relatively high.

We should note that HC and steric FFF are not in competitive positions because the former has been found most applicable to particles 1 μm or less in diameter (*6*), a range overlapping that of normal FFF. However, neither HC nor steric FFF is fundamentally limited to the ranges assigned them, so that overlap is possible in the future.

EXPERIMENTAL

A column for steric FFF was constructed by sandwiching a 0.127-mm Mylar spacer between 12.7 mm thick pieces of plate glass, and clamping the plates together between Lucite bars. The flow channel, cut from the Mylar spacer, had the dimensions 10 mm × 860 mm, giving a channel volume of 1.1 ml. Injection, detection, and collection of samples were the same as for previously reported FFF systems.

The sample particles were glass beads from English Glass Company. These had been previously roughly sized by air elutriation in our labora-

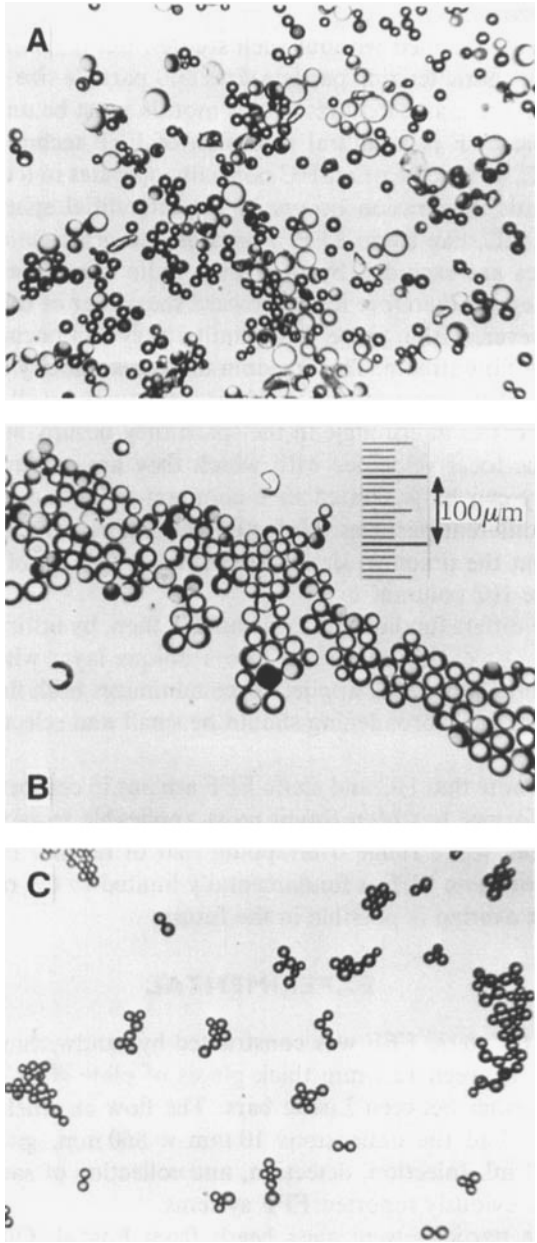

FIG. 2. Photomicrographs of (A) the parent glass bead material and (B) and (C) two samples collected at different intervals during elution from the steric FFF channel.

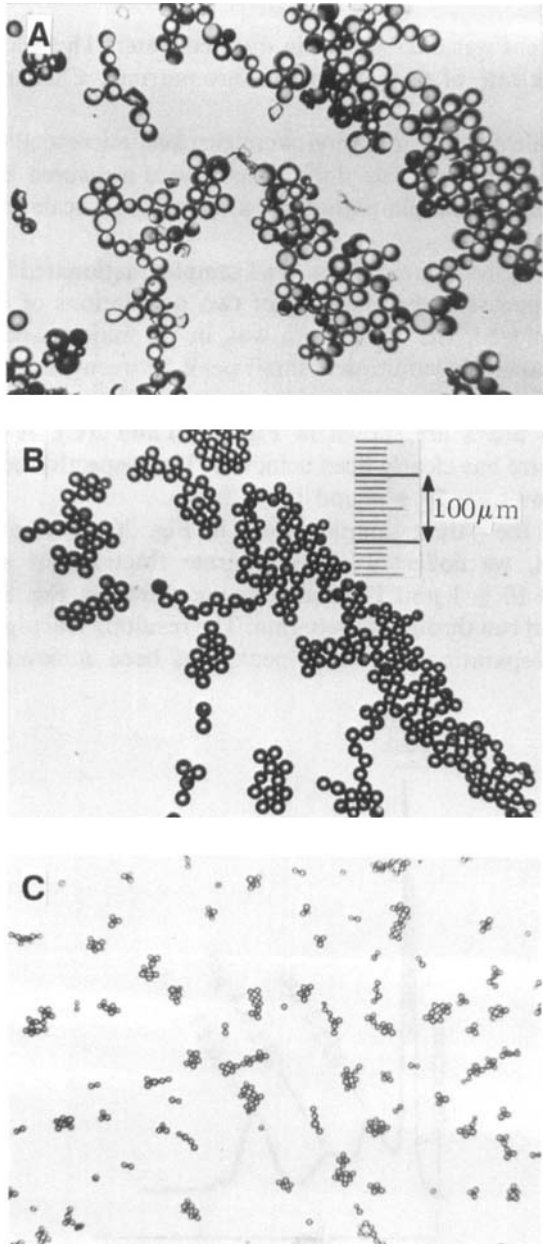

FIG. 3. Photomicrographs of the three different fractions which were subsequently mixed and used to produce the fractogram in Fig. 4.

tory. The solvent was 0.05% SDS in distilled water. This was fed into the channel at the rate of 60 ml/hr by a Chromatronix Cheminert metering pump.

Samples collected upon elution were checked microscopically at 90× and were photographed. Size distributions were measured by comparing the photographs with a photograph of a microscopic scale from National Camera.

Figure 2(A) shows a parent glass bead sample fractionated in our system. The sample appears to be made up of two populations of distinctly different sizes. Indeed, the fractogram was in its major aspects bimodal, although it showed in addition a small peak between the two major size populations. Photomicrographs of beads collected from each of the two major elution peaks are shown in Figs. 2(B) and 2(C). A fractionation according to size has clearly been achieved. The respective bead diameters in the two figures are 29 ± 4 and 19 ± 2 μm.

Using both the parent sample shown in Fig. 2(A) and another set of smaller beads, we collected three separate fractions of sizes 32 ± 3, 23 ± 0.4, and 10 ± 1 μm. The fractions are shown in Fig. 3. These were then mixed and run through the column. The resulting fractogram is shown in Fig. 4. A separation into three peaks has been achieved. Each peak

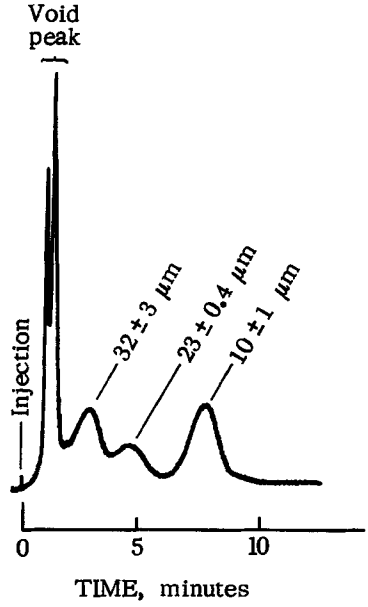

FIG. 4. Fractogram of the three different sizes of glass beads shown in Fig. 3.

emerged at a point corresponding very closely to the point of original collection of the fractionation.

While the above results prove the existence of fractionation, they are preliminary in nature and have been obtained without any attempt at optimization. It is likely that resolution can be considerably improved with further work.

Acknowledgments

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