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Insights from theory and experiments on slip flow in chromatography

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Abstract

Slip flow has become a topic of interest in reversed-phase liquid chromatography because it gives a flow enhancement that facilitates the use of submicrometer particles, providing a large improvement in separation efficiency. Moreover, slip flow provides an additional improvement in efficiency by reducing the velocity distribution in the mobile phase. The phenomenon of slip flow in open tubes is described in chromatographically relative terms. A recent paper in this journal is discussed, as it provides the first theoretical study of slip flow in packed beds, in this case for face-centered cubic geometry. The theory paper reveals that the presence of the packed bed introduces a heterogeneity in fluid velocities that is absent in open tubes, reducing the additional improvement in efficiency from slip flow. The recent paper also suggests that there is yet another factor improving efficiency, which is size-exclusion of proteins from regions of stagnant flow. The latter is supported by recently published data on restricted protein diffusion in face-centered cubic silica colloidal crystals. Extremely low plate heights are enabled by use of submicrometer particles, and further improvement appears to be possible when the analyte size is on the order of 1% of the particle diameter or larger.

Keywords

Efficiency; face-centered cubic crystal (fcc); Protein; Slip

1 Introduction

This commentary regards the recent paper by Drs. Yan and Wang, which presents a much needed theory to describe the reduced plate height and the velocity profiles inside of packed beds for slip flow [1]. By way of background, our own experimental work had previously shown that extremely small plate heights can be obtained in protein reversed-phase liquid chromatography (RPLC) when using nonporous silica particles of 470 nm in diameter. These pack in a face-centered cubic crystalline (fcc) arrangement to eliminate packing heterogeneity [2]. For BSA, we reported a plate height of only 15 nm, which corresponds to a reduced plate height, h , of 0.032. This value was much lower than the minimum reduced

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The corresponding author is part owner of a company that has licensed a patent using slip flow for chromatography columns. The authors have declared no conflict of interest.

plate height, $h_{\min}$, predicted by theory at that time: $h_{\min} = 1.0$ [3] and $h_{\min} = 0.5$ [4]. We had attributed the large discrepancy to slip flow because its narrower velocity distribution would explain the unexpectedly small peak broadening.

While there is a great deal of theory for slip flow in carbon nanotubes [5], the paper of Yan and Wang is the first theory for slip flow in packed beds. The work specifically addresses how much of our reported plate height is from slip flow and how much is just from using a small particle diameter. The results indicate, first, that the reduced plate height even in the absence of slip flow is much lower than what theory had previously been predicted: the new prediction is $h_{\min} = 0.084$. Second, the results indicate that slip flow only modestly improves efficiency, with the plate height decreasing to $h_{\min} = 0.059$ with slip flow. Our experimental result was a factor of two lower than this minimum. The authors attribute our lower value to size exclusion of the protein from regions of stagnant flow.

To discuss this interesting work and its ramifications, we first present a primer on the phenomenon of slip flow. We introduce the concept of slip flow for the case of open capillaries, which is well understood, and then we delve into packed beds, where slip flow is more challenging theoretically. We discuss how slip flow differs between capillaries and packed beds, we cite our recent evidence for size-exclusion of BSA in these media, and we show it to be plausible that the molecular scale dimensions of the theoretical velocity profile allows even this modest amount of size exclusion to appreciably affect the plate height.

2 Slip flow in open capillaries

Slip flow is a phenomenon that becomes important in nanofluidics, where interstitial dimensions are below 100 nm, in contrast to the microfluidic regime where RPLC has been performed. As a consequence, slip flow has been unfamiliar to most chromatographers. Several papers provide a good starting point for learning about slip flow [6–8], and there are interesting observations of extreme slip flow in carbon nanotubes [9–11]. Figure 1 depicts the difference between the familiar parabolic profiles of Hagen–Poiseuille flow in microfluidics versus slip flow in nanofluidics. Both are for the case of open capillaries, where capillary cross-sections are depicted. The slip flow profile of Fig. 1B was drawn simply by taking the parabolic flow profile of Fig. 1A and adding a constant, v_{wall} . It is instructive to ask first why the velocity would go to zero in the familiar case of Hagen–Poiseuille flow. Molecules stop at the wall when they have attractive interactions with the wall. When these attractions are as strong as the attractions with molecules in the fluid, the velocity goes to zero. A zero velocity at the wall is rarely the case, and it is far from the situation in RPLC, where the polar molecules of the mobile phase interact much more strongly with one another than they do with the alkyl stationary phase. The weak attractions between fluid and wall allow a significant nonzero fluid velocity at the wall. This nonzero velocity at the wall is thus an additive component, as drawn in Fig. 1 and written in Eq. (1).

$$v_{\text{slip}} = v_{\text{HP}} + v_{\text{wall}} \quad (1)$$

Equation (1) describes the average velocity, and it explains the most salient manifestation of slip flow: the velocity is larger than one would predict for Hagen–Poiseuille flow. One can

describe the average velocity for Hagen–Poiseuille flow for capillary radius, r_c , pressure, P , viscosity, η , and capillary length, L .

$$v_{\text{HP}} = \frac{P}{8\eta L} r_c^2 \quad (2)$$

This dependence on the square of the capillary radius changes with slip flow. The average velocity in the presence of slip flow is denoted as v_{slip} , which includes the nonzero wall velocity, as given in Eq. (2). Slip flow thus introduces an additive term to the fluid velocity [12].

$$v_{\text{slip}} = v_{\text{HP}} \cdot \left(1 + \frac{4L_s}{r_c} \right) \quad (3)$$

The term L_s is the slip length, which is a property of the interfacial interactions. Weaker interactions give a longer slip length. The slip length dictates the flow enhancement for a given capillary radius, where we use the term flow enhancement, E , to denote the ratio of average velocities, v , or the ratio of volume flow rates, Q .

$$E = \frac{v_{\text{slip}}}{v_{\text{HP}}} = \frac{Q_{\text{slip}}}{Q_{\text{HP}}} = \left(1 + \frac{4L_s}{r_c} \right) \quad (4)$$

It thus follows that the velocity at the wall is a function of slip length, as given in Eq. (5).

$$v_{\text{wall}} = \frac{4v_{\text{HP}}L_s}{r_c} \quad (5)$$

Equation (4) shows that the enhancement would be infinite in the limit of infinite slip length. The slip length is clearly valuable to know if one wanted to design a chromatographic column with enhanced flow, but there is no analytic equation that enables prediction of the slip length. Further, there is wide disagreement in the literature as to the slip length for systems relevant to RPLC, that is, a polar fluid and hydrocarbon wall. Values range from 30 nm to $> 100 \mu\text{m}$ for water flowing past hydrocarbon surfaces, with many results clustered around 50 nm. The disagreements must owe to various parameters that are uncontrolled, such as surface contact angle, parasitic flow, nanoscale bubbles, and surface roughness.

The other parameter important for calculating flow enhancement is the capillary radius, where Eq. (4) shows that slip flow increases with decreasing radius. Figure 2 illustrates why this is the case. To understand the figure, it is necessary to know that the slip length, as defined by Navier in 1823 [13], is the ratio of the velocity at the wall to the shear rate at the wall, which in turn is the ratio of fluid viscosity, η , to the interfacial friction coefficient, ξ_0 .

$$L_s = \frac{v_{\text{wall}}}{(\partial v / \partial r)_{\text{wall}}} = \eta / \xi_0 \quad (6)$$

The two panels in Fig. 2 are drawn for two different radii but the same slip length. The shear rates at the wall are carefully drawn, thus dictating the wall velocities for the fixed slip length. Choosing pressures that give the same maximum velocity, the drawings show that the smaller radius will give a higher v_{wall} for a constant slip length. For this choice of slip length and radius, the wall velocity is about half of v_{max} . The pressure is inconsequential; the wall velocity would always be half of the maximum velocity for this choice of capillary radius and slip length. Mathematically, what necessitates that flow enhancement increases with smaller radius is that the shear rate is in the definition of slip length. Physically, what necessitates more slip flow with smaller radius is the closer proximity of the fluid streams at the wall and the center of the channel. This is why slip flow of liquids is a nanoscale phenomenon.

The drawing of Fig. 2 simplifies by making the maximum velocities the same, necessitating the pressure to be much higher for the smaller radius. Combining Eqs. (2) and (3), one can see that the capillary with the larger radius will always have a higher average velocity for a given pressure.

$$v_{\text{slip}} = \frac{P}{8\eta L} r_c^2 \cdot \left(1 + \frac{4L_s}{r_c}\right) = \frac{P}{8\eta L} \cdot (r_c^2 + 4L_s r_c) \quad (7)$$

Equation (7) also shows that velocity no longer increases with square of the capillary radius on the nanoscale, and as the slip length approaches the capillary radius; the relation between velocity and radius approaches linearity. One can anticipate for packed beds that flow rate will become proportional to particle diameter, instead of the square of the particle diameter, for sufficiently small particles.

Figure 2 also illustrates that the velocity distribution is considerably narrowed for slip flow in an open capillary. The velocity distribution is the issue that is addressed in the theory paper for packed beds. The significance of velocity distribution, of course, is that it determines the C_m mass transport term in the van Deemter equation, which dominates mass transport for nonporous particles and fast adsorption/desorption kinetics.

$$H = A + \frac{2\gamma D}{v} + C_m \cdot v \quad (8)$$

The C_m term is especially a problem for proteins because the slow diffusion of proteins allows less averaging over the radial distribution of velocities. The term $C_m \cdot v$ is proportional to the relative variance in velocity for flow in an open capillary, which can readily be derived for velocities $v(r)$ distributed over the radial positions, r , with probability distribution, $P(r)$, as given in Eq. (9).

$$\frac{\sigma^2}{\langle v \rangle^2} = \int_0^{r_c} \frac{(v(r) - \langle v \rangle)^2 P(r)}{\langle v \rangle^2} dr \quad (9)$$

With reference to Fig. 1, slip only adds a constant to the velocity, thus neither $P(r)$ nor $(v(r) - \langle v \rangle)^2$ are changed by slip, and the relative variance drops by the square of the flow enhancement. The system we used had a fivefold flow enhancement, hence the improvement in c for an open capillary would be a factor of 25. The work of Yan and Wang reveals that a much smaller factor is obtained for packed beds. This is detailed in the next section.

3 Slip flow in packed beds

The discussion thus far has encompassed only the welldefined case of flow in open capillaries, yet virtually all chromatography is performed in packed beds. The theory for open capillaries does not apply to packed beds because the radial dimension of the fluid is undulating and tortuous rather than constant, whereas the flow enhancement depends sensitively on the radial dimension. There has been no theory for slip flow in packed beds, hence the need for the numerical investigation by Yan and Wang.

There is a variety of theoretical tools to describe transport in packed beds, and the tool these authors use is numerical analysis. Theory, of course, always has limitations, and the strategy is to capture the most essential features needed to answer the question. They create perfect fcc crystals in their computer model and impart flow through the crystalline arrangement. Experiment, of course, also has limitations, and the relevant limitation in this case is that the fcc crystals are not perfect. Nonetheless, significant insight can be gained, and we return to these limitations after summarizing their results.

One issue is flow rate enhancement, which is what enables submicrometer particles to be used in a facile way with available pumps. In the absence of slip flow, the velocity through a packed bed is described by the Kozeny–Carman equation, where ε is the porosity of the packed bed [14].

$$\frac{P}{L} = \frac{180 \cdot v \cdot \eta}{d_p^2} \frac{(1 - \varepsilon)^2}{\varepsilon^3} \quad (10)$$

We reported the flow rate of toluene through packed beds of silica particles having a C_4 bonded phase, varying in particle diameter from 125 to 1300 nm, and the behavior fits well to the Kozeny–Carman equation, supporting the expectation that there is negligible slip in this case. For water, once corrected for viscosity, the flow rates were considerably higher, indicating slip flow. The results from our previous paper are reproduced in Fig. 3, where the flow enhancement is plotted versus hydraulic radius, r_{hyd} .

$$r_{\text{hyd}} = \frac{d_p}{3} \frac{\varepsilon}{(1 - \varepsilon)} \quad (11)$$

Hydraulic radius is the ratio of fluid volume to surface area [15]. This is a nonphysical parameter and we used it as an operational parameter in Eq. (3) to calculate an operational slip length in packed beds of varying particle diameter. Pretending the channels to be straight capillaries overlooks the undulations, and we assumed that these details only act to

impart a proportionality constant accounted for in the hydraulic radius. Figure 3 reproduces our published results for silica particles of varying diameter, which were chemically modified to bear a mixed monolayer of C₄ and C₁ [16]. The solid curve is a plot of Eq. (3), using r_{hyd} in place of r_c , and it fits the data well over a wide range of hydraulic radii. The figure also shows the corresponding particle diameters, which span an order of magnitude. The flow enhancement is as high as 20 for 125 nm particles, and is 5 for the 470 nm particles used for the protein separation.

The results of Yan and Wang also show a flow enhancement due to slip flow. They point out that the factor 180 in Eq. (9) applies to random packing. They further show that this factor, which we will denote as f , is 185 for fcc packing, perhaps a consequence of the slightly higher tortuosity. We had used 180, but the difference is negligible within experimental error. They provide an empirical equation that approximates their numerical results, giving f as a function of slip length to account for slip flow.

$$f = 185 \frac{\left(1 + 4.86 \frac{L_s}{d_p}\right)}{\left(1 + 52.6 \frac{L_s}{d_p}\right)} \quad (12)$$

The equation shows that a slip length of zero, that is, no slip, gives $f = 185$, as it must. For a slip length of 63 nm, which was our operational slip length, and for our particle diameter of 470 nm, $f = 38$. This gives a flow enhancement of 5, which is what we observed. Equation (12) gives valuable qualitative insight, showing that packed beds behave differently than open capillaries: flow enhancement does not increase indefinitely. Quantitatively, the equation does not agree with experimentally measured flow enhancements for the smaller diameters plotted in Fig. 3, although it is not clear how far the empirical equation can be extended. The experimental results have considerable credence given their reproducibility over three separate capillaries of each particle diameter, and many measurements for each capillary. It is possible that the numerical analysis does not capture the exact behavior of the flow enhancement over the range of particle diameters used experimentally. Alternatively, it is possible that the change in the amount of fcc order over the range of diameters in the experiments is a factor.

The more pressing issue is whether the relative variance is reduced by the same large factor in a packed bed as it is for an open capillary. The paper of Yan and Wang lends considerable insight into this question. Figure 4, adapted from Yan and Wang's paper, shows a 3D view of the fluid velocities through the fcc packing. The flow is downward, and the velocities are indicated by the color scale. The reduced slip length increases from 0 to 0.05 to 0.5 from parts A, B, and C of the figure, respectively. The images hold average flow rate constant. Focusing on the middle of each image, one can see the effect of slip flow. In part A, which has no slip, the highest velocities (red) are in the center of the channel, and the slowest velocities (blue) are at the particle surfaces. This is just as one would predict from the fluidics of classical LC. Part B shows that the effect of slip flow is to extend the regions of high velocity away from the center, giving a more uniform velocity distribution, as one would expect from the basics of slip flow. Slip flow has put more red color and less blue

color into the image, which translates to a narrower velocity distribution and a higher overall velocity for a given pressure. Part C shows that the highest fluid velocities now extend all the way to the particle surfaces, as one would predict for slip flow in an open capillary, but now a departure from capillary behavior emerges. There remains a region of stagnant flow where the velocity stream hits the particle (blue arrow). The stagnant flow reveals an important point: tortuosity affects the velocity profile for slip flow in packed beds. The consequence is that slip flow cannot entirely eliminate broadening from the velocity distribution in packed beds regardless of slip length. This also explains why the flow rate enhancement does not increase indefinitely. These results from their theory are important contributions to the understanding of slip flow in chromatographic media.

The numerical analysis allows a minimum reduced plate height to be calculated for the limiting cases of no slip versus very large slip, and the results are $h_{\min} = 0.084$ and $h_{\min} = 0.059$, respectively. This comparison shows that tortuosity has a drastic effect on the value of c in slip flow, erasing much of the improvement in plate height one would gain with open capillaries. Nonetheless, the reduced plate height we measured experimentally under slip flow conditions is a factor of two lower, 0.032. We do not know if the theory has a similar quantitative limitation for plate height as it does for flow enhancement. Yan and Wang offer the explanation that our measurement used a rather large protein, BSA, as the analyte, and this protein would be restricted in the velocities it samples. Indeed, we showed experimentally in later work that BSA can sample only 90% of the fluid volume in the packed bed [17]. Further, the excluded volume would be in the very regions where the stagnant flow is: near the particle surfaces. More quantitatively, for the case of a particle having a diameter of 470 nm, the dark blue region of stagnant flow in the centers of Fig. 4B and C extends a distance of about 6 nm from the surface of the particle. Our later work revealed the diameter of BSA in acetonitrile/water to be 7 nm, based on diffusion measurements of BSA in free solution [17]. As a result, the protein is excluded from about half of this stagnant region, thus supporting the interpretation of Yan and Wang. The implication is that improved efficiency can be obtained when the analyte radius is significant relative to the particle diameter. For the case of BSA, the ratio of protein radius to particle radius is 1.5%. Further experiments with varied analyte size will test this idea.

Returning to the limitations of theory and experiments, the experiments necessarily used imperfect fcc crystals. The existence of defects was revealed by the porosity being higher than the theoretical value for fcc: 0.28 instead of 0.26. Our work and a host of other papers on silica colloidal crystals provide SEM images that show fcc domains and grain boundaries. It is reasonable to expect that the additional porosity is from the slight spaces imparted by the grain boundaries. Despite the grain boundaries, the vast majority of particles are inside of fcc crystals, so the theory is probably a good guide even for imperfect fcc crystals.

4 Concluding remarks

The numerical investigations of Yan and Wang provide valuable mechanistic insight into the nature of slip flow in packed beds. Their results show that extraordinary plate heights are possible even without slip flow; their results support the expectation that flow rate is

enhanced by slip flow; and their results reveal that tortuosity mitigates much of the potential improvement in plate height from slip flow. Using particle diameters tailored to the analyte diameter might give a lower plate height by excluding analyte from stagnant regions. The quantitative differences between theory and experiment are now much smaller.

Acknowledgments

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Figure 1. Comparison of velocity profiles in open capillaries for (A) Hagen–Poiseuille and (B) slip flow. The depiction shows that slip flow introduces an additive term to the flow profile, which is a nonzero velocity at the wall.

Figure 2. Narrower capillary radius increases slip flow. The slip length and maximum velocity are identical for the two different radii that are depicted in panels A and B. For the same $v_{\max}$, and slip length, L_s , the shear rate at the wall is necessarily higher for the narrower capillary, giving a higher wall velocity.

Figure 3. Particle size dependence of flow enhancement. Adapted from Rogers and Wirth [16].

Figure 4. False-color flow profiles of fluid velocities through a section of an fcc crystal. Reduced slip lengths: (A) 0, (B) 0.05, and (C) 0.5. The blue arrow in panel C points to a region of stagnant flow, where the particle surface opposes flow. Adapted from supporting information of Yan and Wang [1].