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Einstein's Tea Leaf Paradox and Its Relevance to Dissolution Testing

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In 1926 Einstein explained why tea leaves move to the center of the bottom of a stirred teacup (*1*). In brief, the tea leaves, which follow the motion of the fluid, move in a circular motion while also moving toward the center of the bottom of the cup. This phenomenon is explained in part by the influence of friction between the rotating fluid and the walls and bottom of the cup, causing a decrease in fluid velocity and a resulting spiral inward (*2*). Evidence of the resulting inward flow can be observed in a stirred teacup by the mound of tea leaves at the center of the bottom of the cup after stirring has ceased. The fluid flow toward the center of the bottom of the cup is compensated for by an axial flow upward creating a secondary flow (*2*). The primary and secondary fluid flow patterns for a stirred teacup are depicted in Figure 1 (*3*). Fluid flow in a stirred teacup is not intended as an exact analogy for the complex flow in the USP paddle apparatus where hydrodynamics is affected by the presence of the paddle and its geometry. A major qualitative difference is the presence of recirculation loops both above and below the paddle (*4*). However, the stirred teacup, which is a nontrivial fluid mechanics problem (*5*), does have similarities to the USP paddle apparatus: the accumulation of disintegrated particles beneath the paddle that has been described as coning (*6*), secondary flow patterns that are a component of the flow regime in the USP paddle apparatus (*7*), and instabilities in fluid flow that can cause variation in the exact location of the mound at the bottom of the vessel (*8*). An enhanced understanding of the fluid flow regimes in the USP paddle apparatus has emerged as a result of experimental fluid dynamics (EFD) techniques, such as laser Doppler and particle image velocimetry (PIV) measurements and computational fluid dynamics (CFD) studies (*4*, *7*, *8*). It is clear that the performance of the USP paddle apparatus is linked with and dependent on the inherent physics of flow that, in turn, govern mass transport and dissolution kinetics. The literature (*8*) shows that there are significant variations in fluid velocities within a very small region below the paddle, in and around what is typically referred to as the "dead zone." This is an artifact of the apparatus design itself. As these changes occur within a region where tablets settle after being dropped into the medium, then variations in tablet position can lead to variability in dissolution results. Ideally, if the tablet were to fall at the center of the vessel below the paddle every time, the hydrodynamics it would *see* would always be the same and potentially there would be no hydrodynamics-induced variability on dissolution results.

The preceding discussion is an example of how understanding fluid mechanics can be a stepping-stone to understanding dissolution results. There are instruments such as the USP rotating disk (*9*) and an emerging generation of dissolution testing devices (*10*–*12*) based on fluid mechanics models that avoid secondary flow phenomena. Recent dissolution technologies allow for surface dissolution imaging including the imaging of a single drug crystal (*10*). In other fields, biomedical engineering has also taken a fluid mechanics approach to designing in vitro conditions that provide a hydrodynamic environment relevant to sensitive biological systems such as biofilms (*13*). Since shear created by fluid flow is related to the underlying dissolution process, it is instructive to use the fluid mechanics literature for information about the theory and design of instruments that provide predictable shear under conditions of stable fluid flow. For example, the design of the rotating cone over a stationary plate configuration is based on fluid mechanics principles (*14*). An advantage of this design is that shear stress and shear rate are constant throughout the fluid sample when the gap angle is low and under flow conditions with low values of a dimensionless parameter analogous to the Reynolds number (here defined as a centrifugal to viscous force ratio) (*15*). Although this configuration is not designed for dissolution testing, it does serve as a model that emphasizes the importance of basing instrument design on fluid mechanics principles for the next generation of in vitro dissolution methods for immediate-release solid dosage forms.

The challenge of dissolution testing of immediate-release solid oral dosage forms is to ensure that the dissolution process reflects the physicochemical and mechanical properties of the dosage form that affect dissolution, is reproducible and sensitive to critical quality attributes, and is useful as a tool for correlation with in vivo performance. The key point is that if the hydrodynamic conditions in an apparatus are known, then dissolution data and expectations from the design and quality of the solid dosage form

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Figure 1. Primary and secondary fluid-flow patterns in a stirred teacup.

can be correlated. As was previously mentioned, a difference in dissolution data arising from the tablet position in the USP paddle apparatus can easily be related to the fact that the velocity surrounding the tablet is different for different positions even within a small region of interest.

In summary, it is anticipated that dissolution test methods in the future will continue to depend on the physics of flow for each design. EFD and CFD are tools available for the design of future technologies based on fluid mechanics principles. Using this approach, the intrinsic performance and operating conditions for the design can be established a priori. In effect, the location of the tea leaves at the bottom of the cup will no longer be a factor related to complex fluid dynamics intrinsic to the dissolution testing apparatus.

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