# Using In Vivo Flow Rates in USP Apparatus 4 to Develop a More In Vivo Relevant Hydrodynamic Dissolution Test

**Brian J. Krieg Gordon L. Amidon, and Gregory E. Amidon**
**College of Pharmacy, Department of Pharmaceutical Sciences, University of Michigan**

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

## Introduction

*In vivo* hydrodynamics can impact the rate at which a drug dissolves. One of the main hydrodynamic components is the velocity of fluid flow throughout the gastrointestinal tract. One of the disadvantages of the USP 2 apparatus is the wide variation in velocities observed throughout the apparatus [1]. Also, the peak and bulk velocities (10-20cm/s) are much larger than seen in the intestinal tract (0.02-1cm/s)[2,3]. Therefore a dissolution test that can reduce the magnitude and variation in velocities would be preferred to understand the impact of hydrodynamics on particle dissolution. The USP 4 apparatus allows for relatively uniform fluid velocities in the range present in the intestinal tract which could create a more meaningful hydrodynamic dissolution test. This creates the opportunity to incorporate experimental velocity (particle velocity = (flow rate/area for flow) + settling velocity)/2) through non-dimensional numbers in predicting dissolution rates (eg: Sherwood number).

**OBJECTIVES**

1. Perform dissolution testing of different particles sizes at multiple velocities using the USP 4 apparatus to determine the impact of velocity on the dissolution of a particle.
2. Use the dissolution data to calculate a Sh number that can better define the impact of hydrodynamic properties on dissolution to accurately predict dissolution through using dimensionless numbers

### Dimensionless Number Analysis of Dissolution Results

The particle dissolution was predicted by using the Sherwood number (Sh #) which is a dimensionless number used to describe mass transfer. The Sh # is parameter in the mass transfer coefficient for dissolution of a particle by playing a role in defining the diffusion layer thickness ($h_{eff}$) of a dissolving particle [4] :

$$\frac{dm}{dt} = A\frac{D_{eff}}{h_{eff}}\Delta C; \quad h_{eff} = \frac{d_p}{Sh}; \quad \frac{dm}{dt} = A\frac{D_{eff}\,Sh}{d_p}\Delta C$$

The Sh # is typically defined by the Reynolds number (Re #), and the Schmidt number (Sc #). Additionally there is a diffusion component that is a constant and is typically set to equal 2.The basic format of the Sh # is:

$$Re = \frac{d_p \Delta U}{v};\ \Delta U = \frac{fluid\ velocity + settling\ velocity}{2} \qquad settling\ velocity = \frac{g(\rho_p - \rho_f)d_p}{18\mu} \qquad Sc = \frac{v}{D_{eff}}$$

$$Sh = 2 + aRe^{x}Sc^{1/3}$$

The a and x terms in the Sh # vary in literature with the experimental systems and conditions [5-8]. The diffusion and Sc # component was modeled based on the literature [5-8]. Past experimental work of solid in liquid mass transfer has been focused on modeling a large variation in Re #'s (1- >1,000) which is quite different than a dissolving drug tablet or particle would typically experience in the gastrointestinal tract (Re < 30) [9]. Therefore the experimental data was used to develop a Sh # for smaller particles at lower velocities (Re < 2). It was assumed that the velocity the particle experienced was equal to the fluid velocity during the flow portion of the USP 4 pumping pulse and equal to the particle settling velocity during the no flow portion of the pulse. Therefore the velocity is dependent on particle size and density.

## Methods:

The dissolution of 10mg of ibuprofen particles was studied using the Sotax CE-7 USP apparatus 4 with 12mm powder cell. Three different sieve cuts were studied with mean particle diameters (d) of 45, 111, and 235µm. The true density of the ibuprofen particles was measured to be 1.118mg/ml. Each of the sieve cuts was studied at flow rates of 11 and 25ml/min. Additionally, the 45 and 111µm sieve cuts were also studied at 6ml/min. 10mg of the ibuprofen particles were introduced into the USP 4 Cells as part of a 20mg/ml ibuprofen/1.5% Avicel/0.75mM sodium dodecyl sulfate (SDS) suspension. The dissolution medium consisted of 550ml of 0.75mM SDS, pH 4.5, 50mM acetate buffer (ibuprofen solubility =0.15mg/ml). MATLAB was used for dissolution simulations.

## Results

Figure 1. shows the calculation for the Sh # based on the results for each experimental condition. The results were evaluated at 50% dissolved to calculate the experimental Sh#. The Sh # was chosen based on the best fit for the entire data set and it was found to be Sh = 2+1.89ReSc$^{1/3}$. This Sh # was used for all of the particle dissolution predictions.

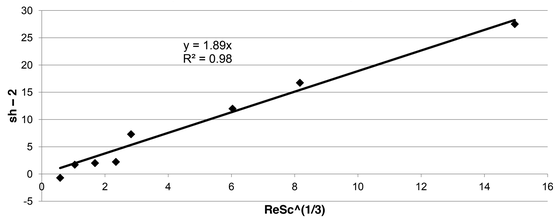


**Figure 1. The calculated experimental Sh #'s as a function of ReSc$^{1/3}$. Key (◆) Experimental data; (——— ) Best fit trendline to predict the impact of the Re # on Dissolution;**

Figure 2. shows how the Sh # changes with particle size and flow rate. A large particle at a high flow rate will have a large Sh # due to the Re #. As the particle size decreases the dissolution becomes less affected by hydrodynamics and more of a diffusion controlled process (Sh = 2).

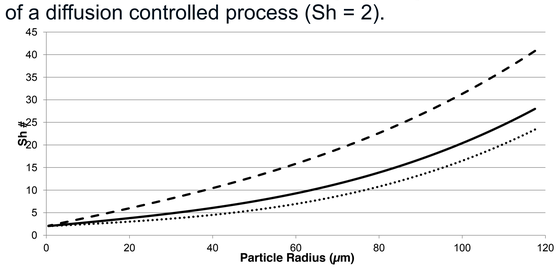


**Figure 2. Calculated Sh #'s based on the best fit data and as a function of particle size and flow rate. Key (····· ) Calculated Sh #'s for a flow rate of 6ml/min; (——— ) Calculated Sh #'s for a flow rate of 11ml/min; ( – – ) Calculated Sh #'s for a flow rate of 25 ml/min;**

Figure 3. shows the impact of velocity and particle size on the diffusion layer thickness. Increasing the velocity decreases the thickness of the diffusion layer. However, the settling velocity and therefore the average velocity is a function of particle size and it is decreasing as the particle dissolves. This leads to the diffusion layer thickness increasing as the particle is dissolving until a particle radius of ~50µm. At particle radius of ~50µm the particle size is decreasing faster than the velocity (i.e. Re and Sh#). Therefore the diffusion layer thickness starts decreasing for ibuprofen particles< 50µm.

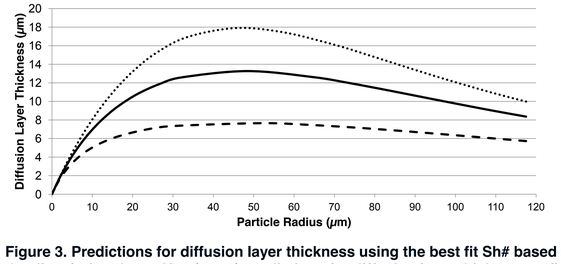


**Figure 3. Predictions for diffusion layer thickness using the best fit Sh# based on the dissolution data. Key (····· ) predictions for diffusion layer thickness at flow rate of 6ml/min; (——— ) predictions for diffusion layer thickness at flow rate of 11ml/min; ( – – ) predictions for diffusion layer thickness at flow rate of 25ml/min;**

## Results (Continued)

Figure 4. Shows the experimental and predicted results for the dissolution of 45µm ibuprofen particles in the USP 4 apparatus at flow rates of 6ml/min, 11ml/min, and 25ml/min. The experimental and predicted results show that as the flow rate is increased, the dissolution rate of the particles increases as well. The experimental data shows a large variation in the results. The predictions do a fairly good job at predicting the data at the higher flow rates but it does not do a good job at predicting the 6ml/min flow rate data. The large variation in the low flow rate could be due to the particles not being dispersed well enough which could lead to the particles agglomerating and forming larger particles which take longer to dissolve.

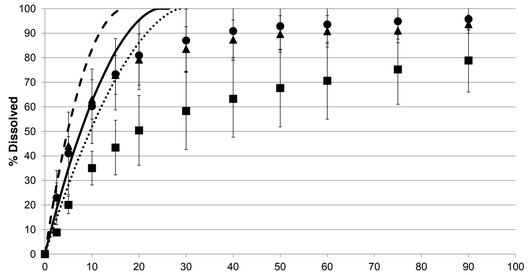


**Figure 4. USP 4 dissolution results of 45µm ibuprofen particles in 50mM Acetate buffer at pH 4.5 and at 37°C. Key (■ ) experimental dissolution at a flow rate of 6ml/min; (⬮ ) experimental dissolution at a flow rate of 11ml/min; (▲ ) experimental dissolution at a flow rate of 25ml/min; (·····) predicted dissolution at 6ml/min; (———) predicted dissolution at 11ml/min; ( – – ) predicted dissolution at 25ml/min;**

Figure 5. Shows the experimental and predicted results for the dissolution of 111µm ibuprofen particles in the USP 4 apparatus at flow rates of 6ml/min, 11ml/min, and 25ml/min. The predictions do a good job of accurately predicting the dissolution of the particles at all of the flow rates. The 6ml/min flow rate data displays a lot of variation in the data similar to the 45um data and again this could be caused by particles agglomerating which is likely more prevalent at lower flow rates.

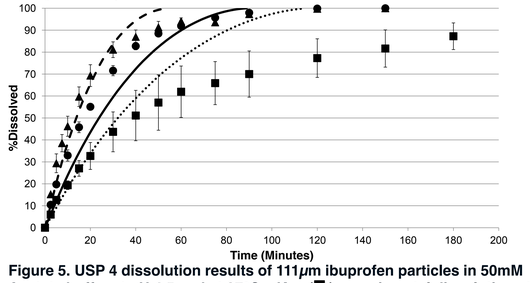


**Figure 5. USP 4 dissolution results of 111µm ibuprofen particles in 50mM Acetate buffer at pH 4.5 and at 37°C. Key (■ ) experimental dissolution at a flow rate of 6ml/min; (⬮ ) experimental dissolution at a flow rate of 11ml/min; (▲ ) experimental dissolution at a flow rate of 25ml/min; (·····) predicted dissolution at 6ml/min; (———) predicted dissolution at 11ml/min; ( – – ) predicted dissolution at 25ml/min;**

Figure 6. Shows the experimental and predicted results for the dissolution of 235µm ibuprofen particles in the USP 4 apparatus at flow rates 11ml/min and 25ml/min. The experimental results show a large amount of variation. However, the particle dissolution model accurately predicts the average dissolution at each of the flow rates.

## Results (Continued)

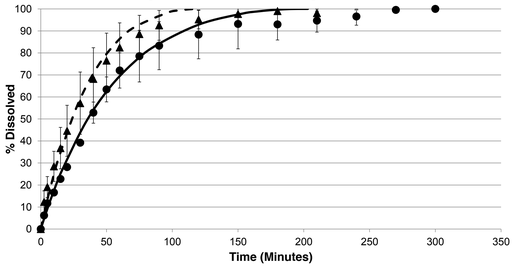


**Figure 6. USP 4 dissolution results of 235µm ibuprofen particles in 50mM Acetate buffer at pH 4.5 and at 37°C. Key (⬮ ) experimental dissolution at a flow rate of 11ml/min; (▲ ) experimental dissolution at a flow rate of 25ml/min; (——— ) predicted dissolution at 11ml/min; ( – – ) predicted dissolution at 25ml/min;**

## Conclusions

- The USP 4 apparatus offers a more well defined velocity profile that is in the range of what is physiologically relevant and allows for accurate predictions to be made. However, there is a large amount of experimental variation caused by possible particle agglomeration or particles forming a cake at the top of the cell

- The experimental and predicted data shows that velocity has an impact on dissolution (and diffusion layer thickness). However, as the particle size decreases so to does the impact of velocity and dissolution becomes a diffusion controlled process.

- The settling velocity in the USP 4 apparatus seems to play a significant role for large particles at low flow rates and more work needs to be done to see how effectively this model can be applied to particles with different densities and solubilities.

**ACKNOWLEDGEMENTS**

Financial support was provided by: AstraZeneca,
The United States Pharmacopeia Fellowship: 2010-2012, and
Chingju Wang Sheu Graduate Student Fellowship 2010-2011

### References

1.)Bai G, Wang Y, Armenante PM 2011. Velocity Profiles and Shear Strain Rate Variability in the USP Dissolution Testing Apparatus 2 at Different Impeller Agitation Speeds. International Journal of Pharmaceutics 403:1-14.
2.) Pal A, Indireshkumar K, Schwizer W, Abrahamsson B, Fried M, Brasseur JG 2004. Gastric flow and mixing studied using computer simulation. Proceedings of the Royal Society B: Biological Sciences 271(1557):2587-2594.
3.) Gutzeit A, Patak MA, Weymarn Cv, Graf N, Doert A, Willemse E, Binkert CA, Froehlich JM 2010. Feasibility of Small Bowel Flow Rate Measurement With MRI. Journal of Magnetic Resonance Imaging 32:345-351.
4.) Sugano K 2008. Theoretical comparison of hydrodynamic diffusion layer models used for dissolution simulation in drug discovery and development. International Journal of Pharmaceutics 363(1-2):73-77.
5.)Ranz WE, Marshall WR 1952. Evaporation From Drops: Part II. Chemical Engineering Progress 48(4):173 - 180.
6.)Garner FH, Grafton RW 1954. Mass Transfer in Fluid Flow from a Solid Sphere. Proceedings of the Royal Society of London Series A, mathematical and Physical Sciences 224(1156):64-82.
6.)Garner FH, Suckling RD 1958. Mass Transfer from a Soluble Solid Sphere. AIChE Journal 4(1):114-124.
8.)Steinberger RL, Treybal RE 1960. Mass Transfer From a Solid Soluble Sphere to a Flowing Liquid Stream. AIChE Journal 6(2):227-232.
9.) Abrahamsson B, Pal A, Sjoeberg M, Carlsson M, Brasseur JG, et al. 2005. A novel in vitro and numerical analysis of shear-induced drug release from extended-release tablets in the fed stomach. Pharmaceutical Research 22(8):1215-1226.