Influence of Fluid Shear Rate on the Dissolution Rate of Poorly Soluble Drug Particles; Implications for *In Vivo* Predictive *In Vitro* Dissolution Methodologies and Mechanistic Computational Modeling

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PURPOSE

Recent mass transport analysis using computational fluid dynamics indicates that the fluid shear rate local to a drug particle creates significant hydrodynamic enhancement to dissolution rate over pure diffusion, even for "small" particles (below ~100-200 µm diameter) and in the intestines, with much lower shear rates than a USP 2 dissolution device, distinguishing *in vivo* from *in vitro* dissolution (**Figures 1 & 2**)[1]. Wang & Brasseur used accurate computer data to develop empirical relationships between non-dimensional mass flux (Sh) and shear Peclet and Reynolds numbers (S*, Re_S). The USP 2 *in vitro* dissolution test method typically creates shear rates 2-3 orders of magnitude higher than what is expected *in vivo* in the fed-state (based on computer simulation), greatly enhancing *in vitro* versus *in vivo* dissolution rate for drugs with low *in vivo* BCS II/IV solubility (**Figure 2**). THE AIM OF THIS STUDY is to experimentally assess the impact of fluid shear rate on particle dissolution rate *in vitro* under conditions of well-defined shear in a Couette flow device consistent with dissolution both *in vivo* (in the fed state intestines) and *in vitro* (in normal operation of the USP 2 apparatus).

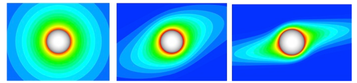

Figure 1: Patterns of scalar concentration around a spherical particle in a simple shear flow at $Re_s=SR^2/\nu$ =0.1 and three $S^*=SR^2/D_m$ values where S = shear rate, R = particle radius, ν = fluid kinematic viscosity and D_m = diffusion coefficient[1].

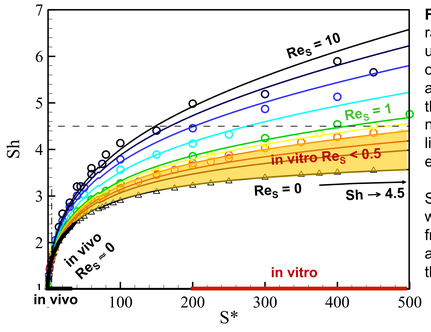

Figure 2: Influences of shear-rate (S*) on dissolution-rate (Sh) under conditions representative of an *in vitro* USP 2 apparatus and the human small intestine in the fed state. Open circles are numerical simulations and solid lines show the corresponding empirical correlations[1].

$Sh=N_s''R/[D_m(C_s-C_b)]=R/\delta$, where N_s'' is mass flux of drug from the particle surface and δ is a properly defined diffusion layer thickness[4].

METHODS

A Couette flow device comprising a Brookfield viscometer and recirculating water bath was chosen for the *in vitro* dissolution experiments so shear rate could be carefully controlled. Drug particles dissolve in a dissolution medium contained within the space between two concentric cylinders, one moving relative to the other (**Figure 3**). Controlled, well-defined shear rates at values of interest were achieved in a dissolution test medium, which was density matched to the drug particles to minimize particle settling. Benzoic Acid was chosen as the model compound due to its low solubility in the dissolution medium (**Table 1**). Bulk Benzoic Acid powder was sieved to create three different particle size distributions. For each particle size distribution, volume-averaged radius (R_{avg}) based upon an equivalent sphere was determined using a Nikon optical microscope with a SPOT camera and imaging software (**Table 2**). Dissolution experiments were performed at shear rates relevant to the human small intestine (S* = 4.2) and the *in vitro* USP 2 apparatus (S* = 312 – 6270). Dissolved Benzoic Acid concentrations were measured at specified time points using a StellarNet UV-Vis spectrometer with fiber optic probe.

Table 1: Properties of Benzoic Acid and Density Matched Solution (DMS) test medium

BCS Class	1
Molecular mass	122.12 g/mol
Intrinsic solubility (25°C)	3.2 mg/ml [a]
Solubility in DMS (20°C)	0.385 mg/ml [b]
pK_a (25°C)	3.99 [a]
LogP	1.96 [a]
Particle true density	1.29 g/cm^3 [b]
Diffusion coefficient in DMS (20°C)	8.4 X 10^{-7} cm^2/s [c]
Particle shape	Columnar [b]
DMS composition	3.8 M NaH_2PO_4 30 µM SDS
DMS viscosity (20°C)	6.7 cP [b]

[a] Ref. 2 [b] Measured in our laboratory
[c] Estimated using Ref. 3

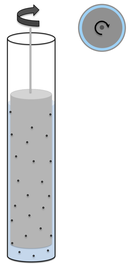

Figure 3: (Left) Side view of Couette flow system. Dose of 5 mg Benzoic Acid particles in 12 ml of DMS controlled at 20°C.

(Right) Top view of Couette flow system. Rotating inner cylinder and stationary outer cylinder. DMS contained between gap (gap width of 1.2 mm)

Table 2: S, S* and Re_s at start-up for each R_{avg} used in the Couette flow experiments

R_{avg}	(µm)	26	50	71	50	71
S	(s^{-1})	0.5	11	11	106	106
S*		4.2	312	627	3120	6267
Re_s	(X 10^2)	0.01	0.5	1.1	5.2	10.5

RESULTS

Dissolution rate is greatly enhanced in the presence of both *in vivo* and *in vitro relevant* shear rate relative to pure diffusion (S* = 0) **(Figure 4)**. Shear enhancement is significantly less under shear rates relevant to the human small intestine (S* = 4.2) compared to the *in vitro* USP 2 apparatus (S* = 312 – 6270). When bulk concentration normalized by solubility (C_s/C_b) is plotted against time normalized by time for the mean particle to dissolve in sink conditions (t/τ_{diss}), dissolution rate stratifies according to normalized shear rate S*. Predictions using a polydisperse model[4] extended to include the correlation with shear rate deduced by Wang et al. (2013) compare reasonably well with the measurements, with differences that depend on the assumed polydisperse distribution (here approximated using a Gaussian fit to the microscopy data). The effect of shear causes the bulk concentration to be larger by factors of 2-4 during dissolution in the presence of fluid shear rate when compared to pure diffusion.

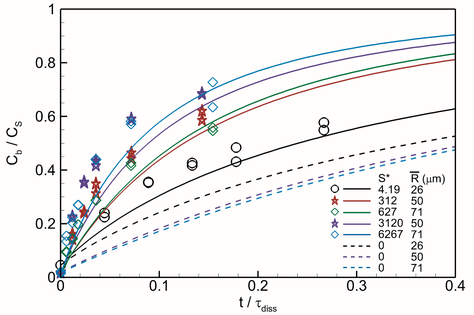

Figure 4 : Benzoic Acid Couette flow experimental results (data points) with predictions (lines; using correlations within a "hierarchical" extension to a quasi-steady state model[4]).

CONCLUSIONS

The results of this study show major enhancements in particle dissolution rate due to local fluid shear rate acting on Benzoic Acid particles under controlled test conditions. Presentation of the results in properly normalized form indicates general applicability to other drugs in other dissolution environments[4]. Results of this study can be used to help define drug particle properties where fluid shear is important to particle dissolution and could be used to help define expected dissolution performance in a USP 2 apparatus representative of high shear rates compared to the shears in the fed human intestine. The influence of local shear rate is shown to be a strong hydrodynamic influence on drug dissolution.

REFERENCES & FUNDING

1. Brasseur JG and Wang YX, *Bull Amer Phys Soc*; 2013, 58 (manuscript in preparation) **2.** Avdeef A, Berger CM, *Eur J Pharm Sci;* 2001, 14: 281-291, DOI: 10.1016/S0928-0987(01)00190-7 **3.** Hayduk W, Laudie H, *AIChE J*; 1974, 20: 611-615, DOI: 10.1002/aic.690200329 **4.** Wang YX, Abrahamsson B, Lindfors L, Brasseur JG, *J Pharm Sci*; 2015, 104: 2998-3017, DOI: 10.1002/jps.24472.

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