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 fluid shear rate is a dominant hydrodynamic effect that enhances dissolution rate over pure diffusion for particles less than ~100-200 μm in diameter in the intestine and distinguishes *in vivo* from *in vitro* dissolution (Brasseur & Wang, 2013). The USP II *in vitro* dissolution test method, for example, is performed under conditions with shear rates 2-3 orders of magnitude higher than what is expected *in vivo* in the fed-state, greatly enhancing *in vitro* vs. *in vivo* dissolution rate for drugs with low *in vivo* solubility (BCS 2 and 4). The aim of this study was 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* and in the USP II apparatus.

Methods

A Couette cell system comprising a Brookfield viscometer and recirculating water bath was chosen for the *in vitro* dissolution experiments, where drug particles dissolve in a dissolution medium contained within the space between two concentric cylinders, one moving relative to the other. Controlled, well-defined shear rates at values of interest were achieved in a dissolution test medium 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 (385 ug/ml). Bulk benzoic acid powder was sieved to create three different initial particle size distributions having volume-average radii (R) of 26, 50 and 71 μm, as determined by microscopy. Dissolution experiments were performed at a shear rate of 0.6 s^{-1} for R equal to 26 μm and at shear rates of 11 s^{-1} and 106 s^{-1} R equal to both 50 and 71 μm. For all experiments dose-to-volume ratio (total concentration) was 0.42 mg/ml and temperature was controlled to 20 C. Diffusivity (D_m) estimated using the Hayduk-Laudie equation was unusually low (8.47×10^{-7} cm^2/s) due to the high viscosity (6.7 cP) of the density-matched solution. Dissolved benzoic acid concentrations were measured at specified time points using UV-Vis spectroscopy. Linear regression modeling using the statistical software R was performed to determine the statistical significance of shear rate on dissolution rate.

Results

The rate of dissolution was faster for the high compared to the low shear rate at a given value of R. For R equal to both 50 and 71 μm, dissolved concentration was increased by 50% after both 10 and 20 min of dissolution. When bulk concentration normalized by solubility is plotted against time normalized by the time for the mean particle to dissolve in sink conditions, the dissolution stratifies according to the shear rate normalized by D_m/R^2. Shear rate as well as R were found to have statistically significant impacts on dissolution rate. Linear regression analysis demonstrated that a 10 s^{-1} increase in shear rate should cause a 4.0 μg/ml increase in dissolved drug concentration (controlling for all other variables) for benzoic acid under the conditions tested. Predictions using a polydisperse model (Wang et al., 2015) 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. 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.

Conclusions

The results of this study show major increases in particle dissolution rate as a function of fluid shear rate for benzoic acid particles under the conditions tested. The importance of shear rate enhancement over pure diffusion for additional compounds and in additional in vitro apparatuses is currently unknown. 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.

References

Brasseur, J.G., Wang, Y. 2013 Hydrodynamic Enhancements of Dissolution from Drug Particles: *In vivo* vs. *In vitro*. (abstract) Bull. Amer. Phys. Soc. 58 (18): http://meetings.aps.org/link/BAPS.2013.DFD.D16.3.

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