FY 2016 Generic Drug Research
FDA Public Hearing
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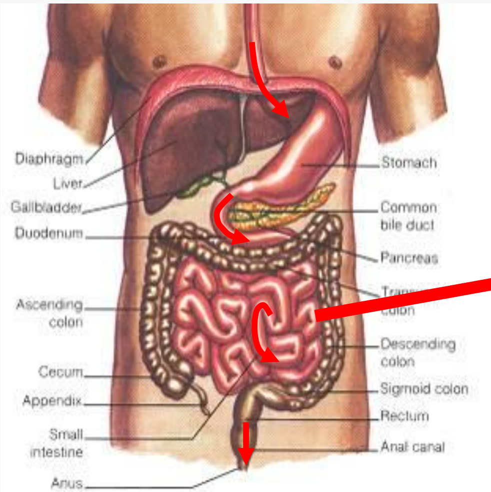
Importance and Modeling of Hydrodynamic Effects in Dissolution and Absorption *In Vivo* vs. *In Vitro*

James G. Brasseur, Ph.D.

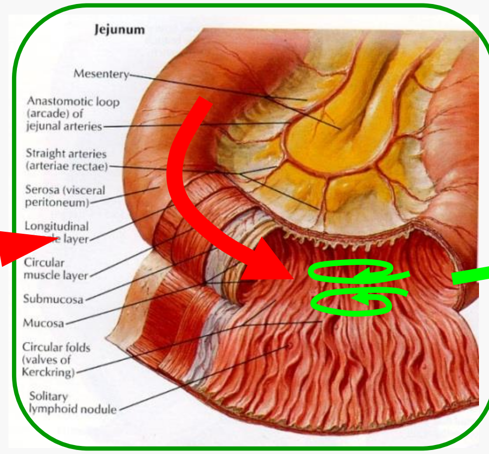
Research Professor, Aerospace Engineering Sciences
University of Colorado Boulder

Emeritus/Adjunct Professor of Mechanical Engineering, Bioengineering and Mathematics
Pennsylvania State University

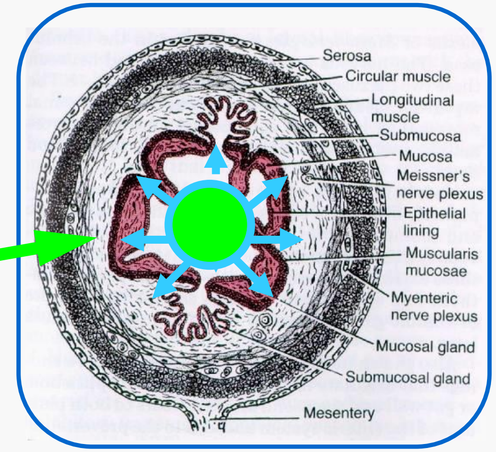
Intestinal vs. *In Vitro* Hydrodynamics



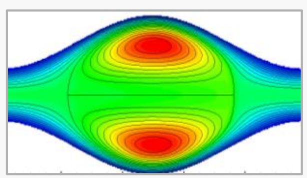
Intestinal Hydrodynamics: Transport, Mixing, Absorption

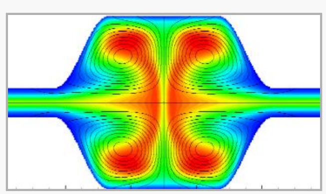


MACRO: Mixing at the Lumen Scale



MICRO: Mixing and Absorption at Mucosa

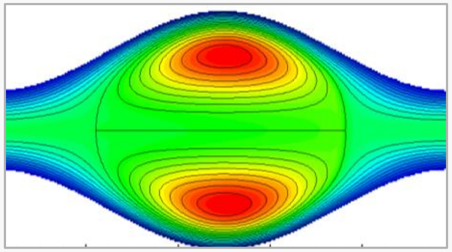


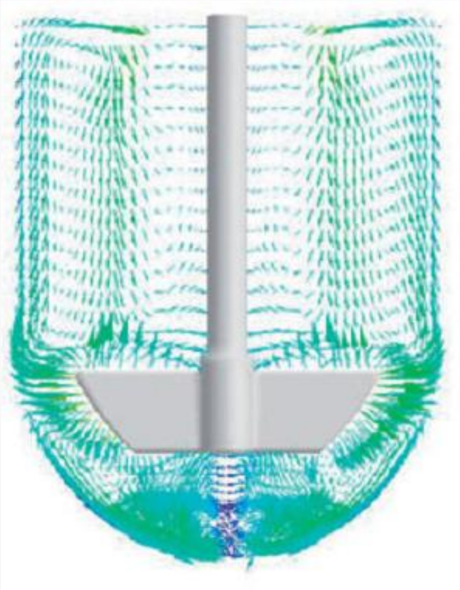


Intestinal vs. *In Vitro* Hydrodynamics

Peristaltic Contractions (propagating waves)

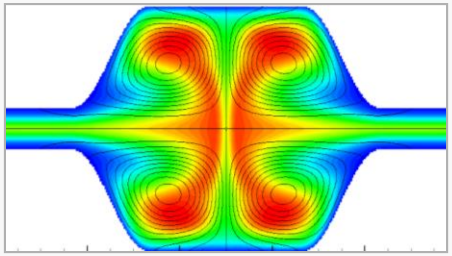
(axial transport)





Segmental Contractions (standing waves)

(radial mixing)

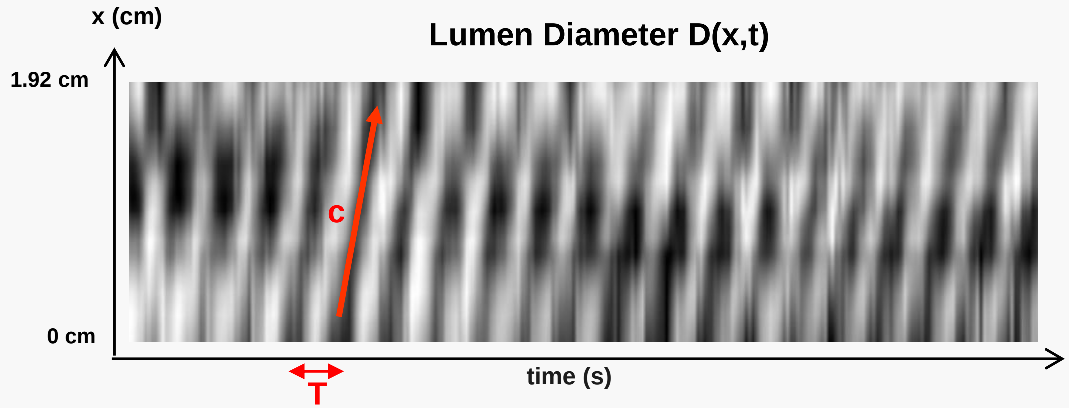


Videofluoroscopy of dog intestine by H. J. Ehrlein
(http://www.wzw.tum.de/humanbiology/)

Lumen-Scale Motility in the Intestines

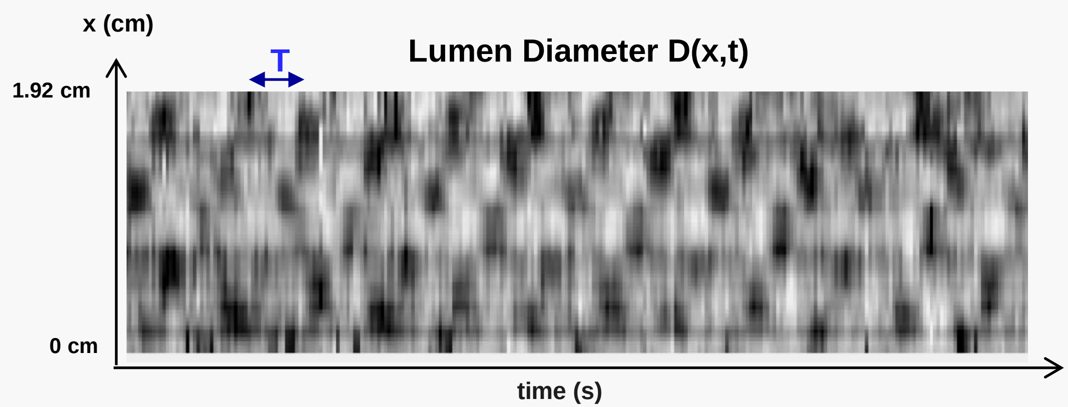
- Fed State -

Peristaltic Contractions

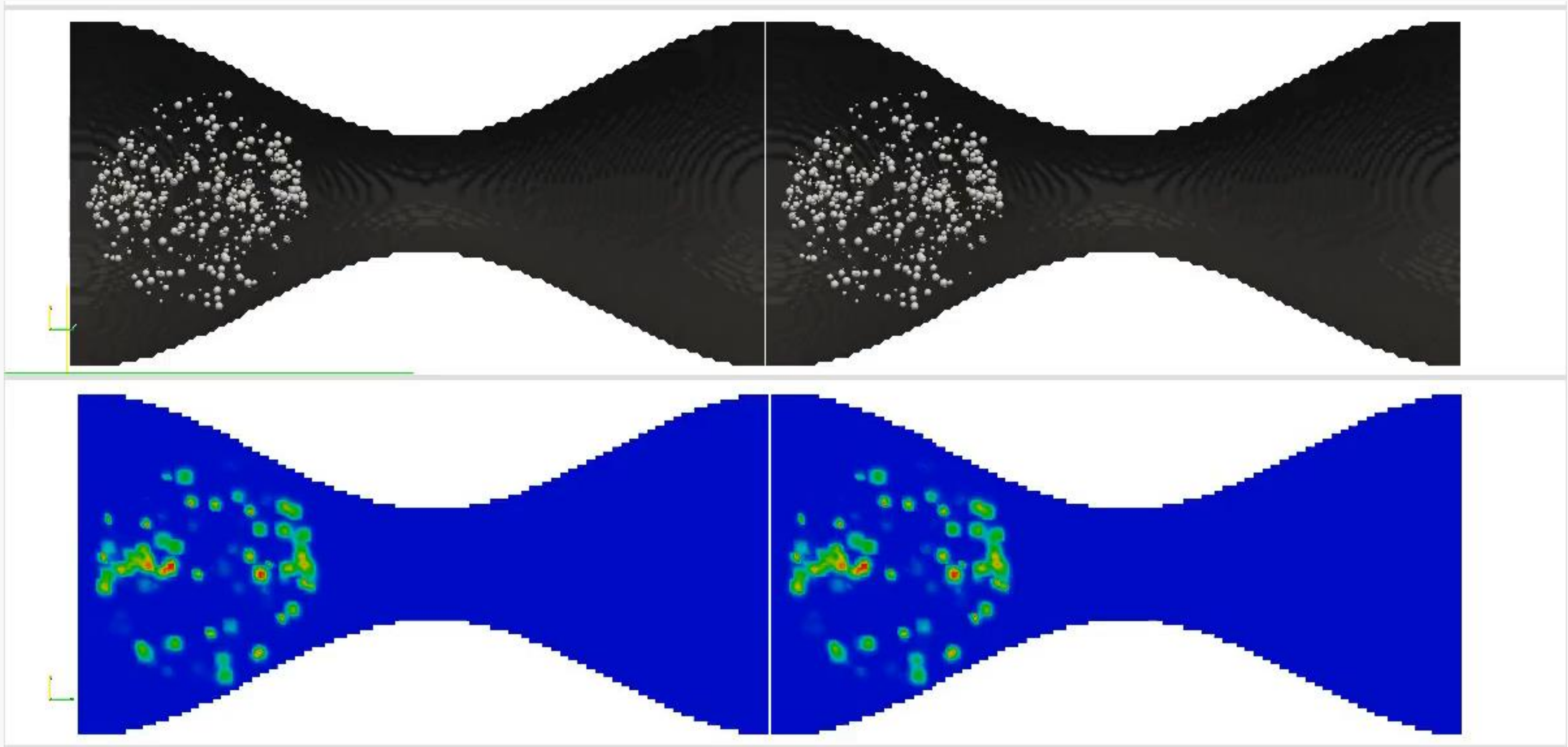


c ~ 1-3 mm/s
T ~ 2-4 s
(also humans)

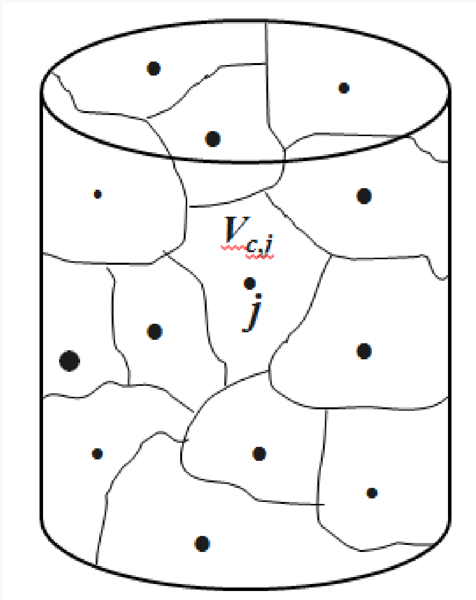
Segmental Contractions



In Vivo Hydrodynamics for Drug Dissolution



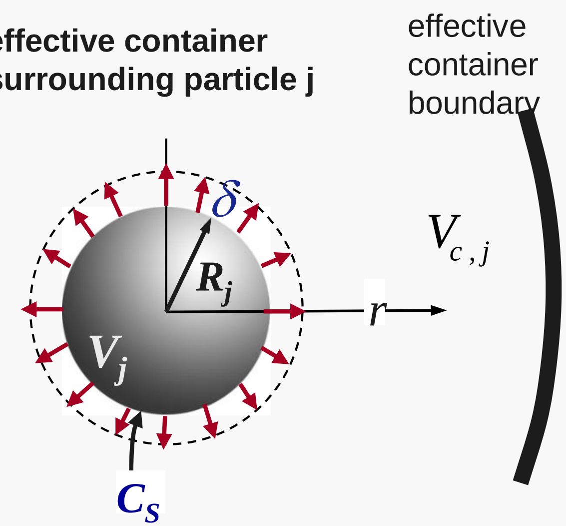
Modeling Hydrodynamic Influences on Dissolution Rate



$$\frac{dR_j(t)}{dt} = -\upsilon_m D_m \frac{[C_S - C_{b,j}(t)]}{R_j(t)} Sh_j(t)$$

$$Sh_j = 1 + \Delta_{confinement} + \Delta_{hydrodynamics}$$

effective container surrounding particle j



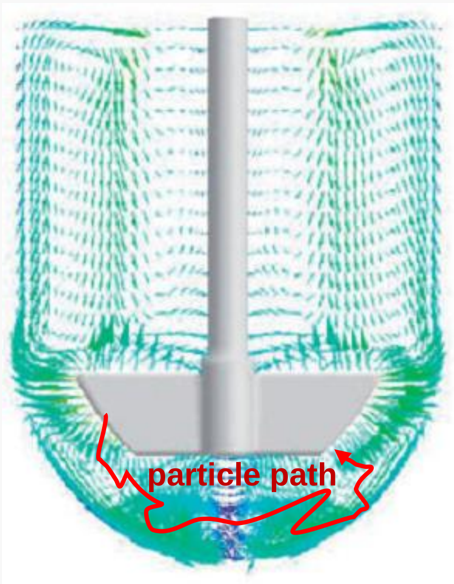
Hydrodynamic Enhancements to Dissolution:

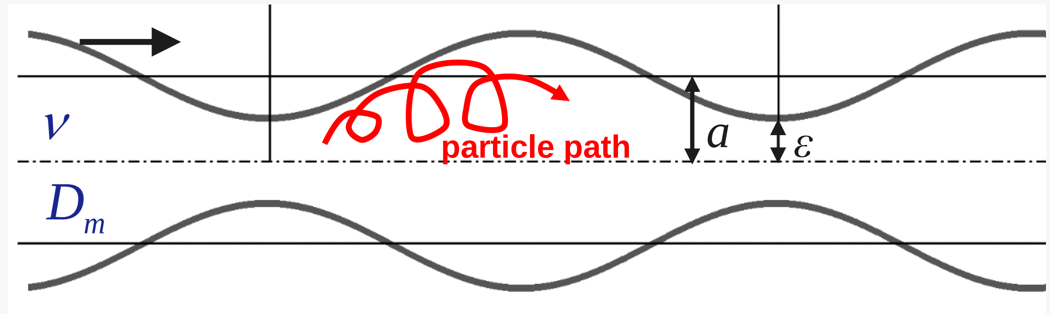
1/ Convection

2/ Flow Shear

In vivo vs. In vitro?

Hydrodynamics, *In Vivo* vs. *In Vitro*: Convection (Slip)





Hydrodynamic Particle Parameters for Dissolution Rate

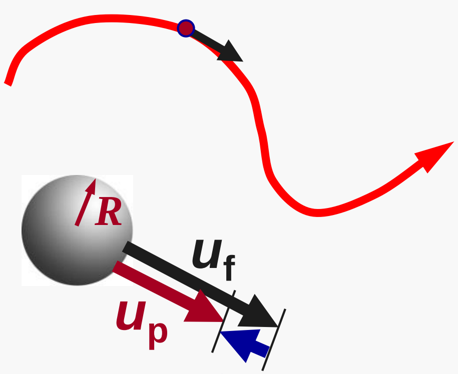
$$\mathrm{Re}_{\Delta u} = \frac{(\Delta u)R}{\nu}$$

Slip Velocity "Reynolds Number"

$$\mathrm{Pe}_{\Delta u} = \frac{(\Delta u)R}{D_m}$$

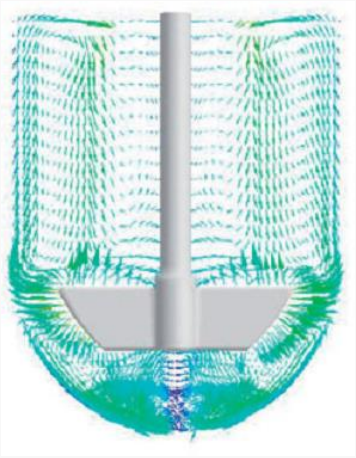
Slip Velocity "Peclet Number"

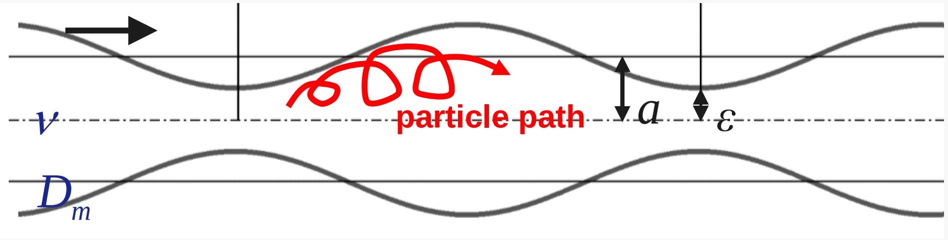
particle path



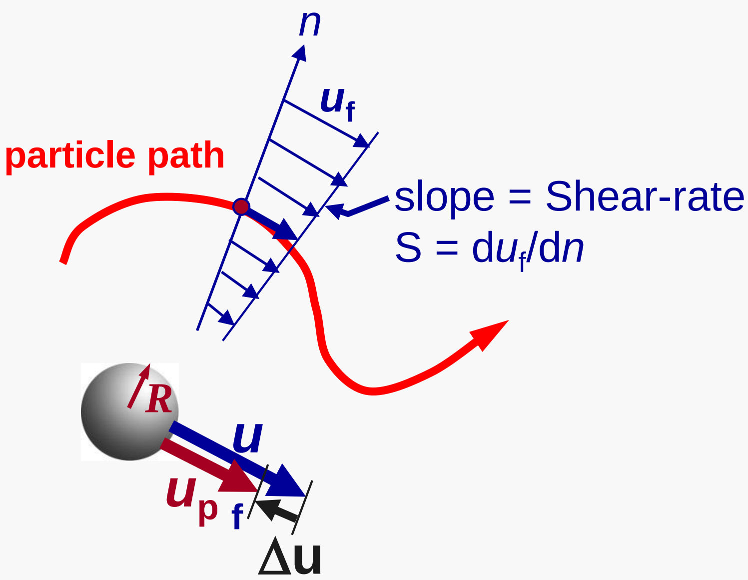
Δu ⇐ slip velocity

A Previously Unappreciated Hydrodynamic Effect on Dissolution Rate: Fluid Shear





Hydrodynamic Particle Parameters for Dissolution Rate



$$\mathrm{Re}_{\Delta u} = \frac{(\Delta u)R}{\nu}$$ Slip Velocity Reynolds Number

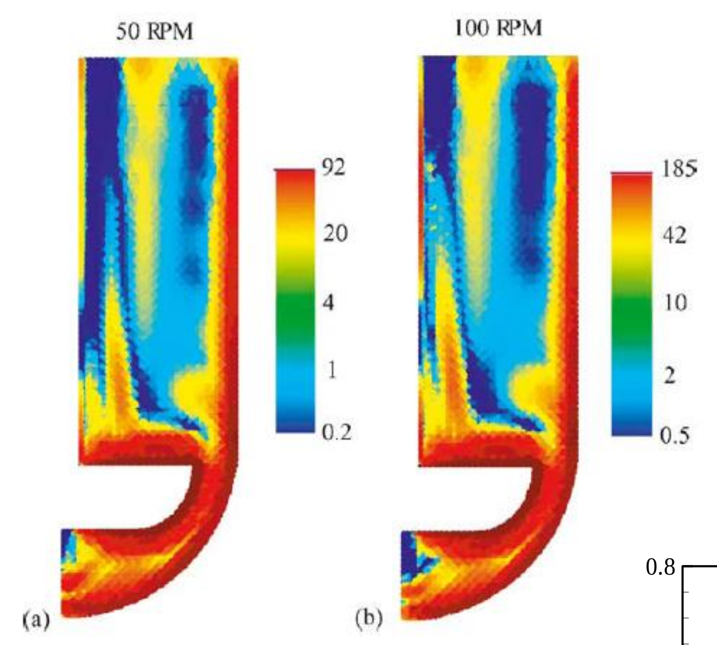
$$\mathrm{Pe}_{\Delta u} = \frac{(\Delta u)R}{D_m}$$ Slip Velocity Peclet Number

$$\mathrm{Re}_S = \frac{SR^2}{\nu}$$ Shear Reynolds Number

$$S^* = \frac{SR^2}{D_m}$$ Shear Peclet Number

Shear Rate: *In Vitro* USP II vs. *In Vivo* Intestine

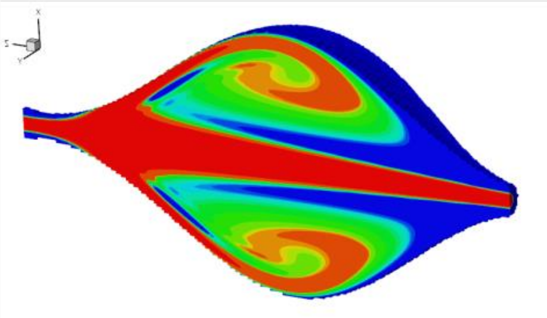
USP II, Computer Simulation*

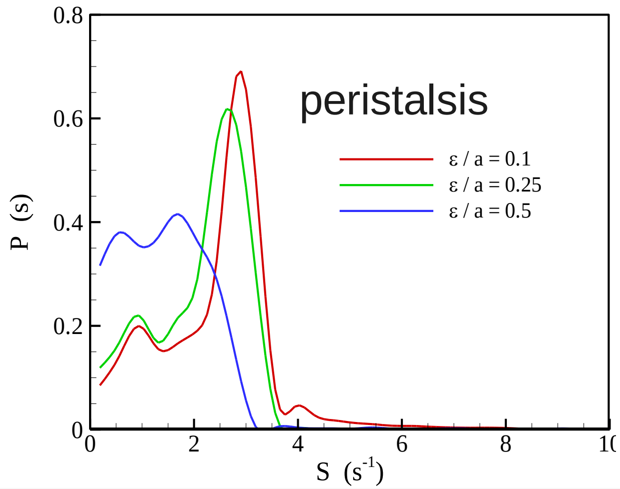


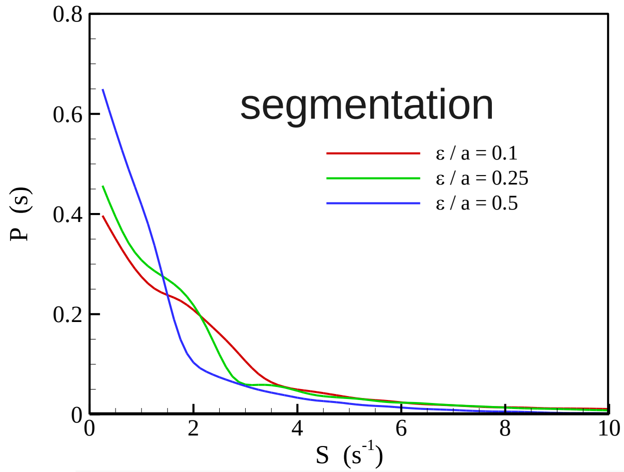
Distribution of shear rates within the media at 50 and 100 rpm

*J. Kukura, J. Baxter, and F. Muzzio, *Int. J. Pharm.*, 279 (2004) 9-17; from Computational Fluid Dynamics

GUT,
Computer Simulation**

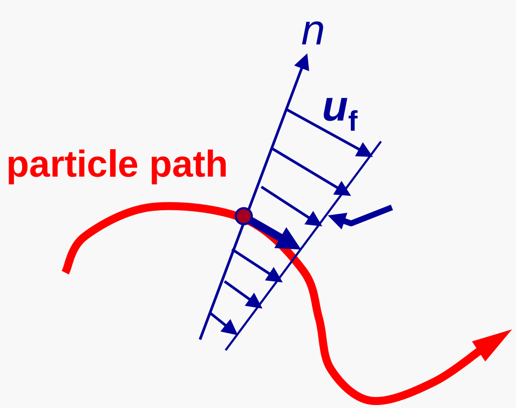


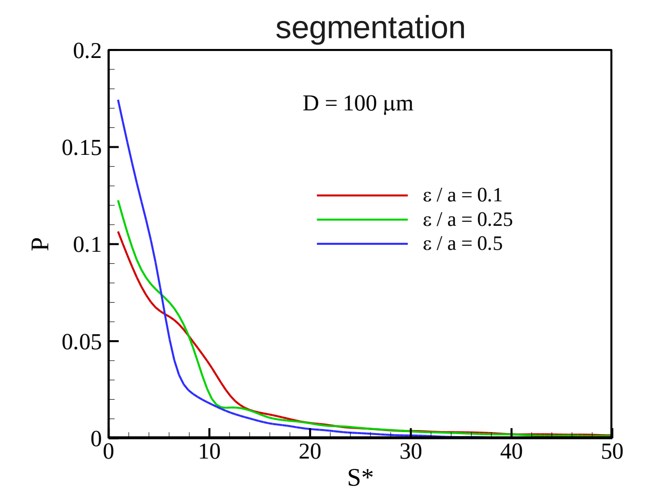




**Wang & Brasseur

Shear Parameters with Shear: Intestine vs. USP II





$$Re_S = \frac{SR^2}{\nu}$$

$$S^* = \frac{SR^2}{D_m}$$

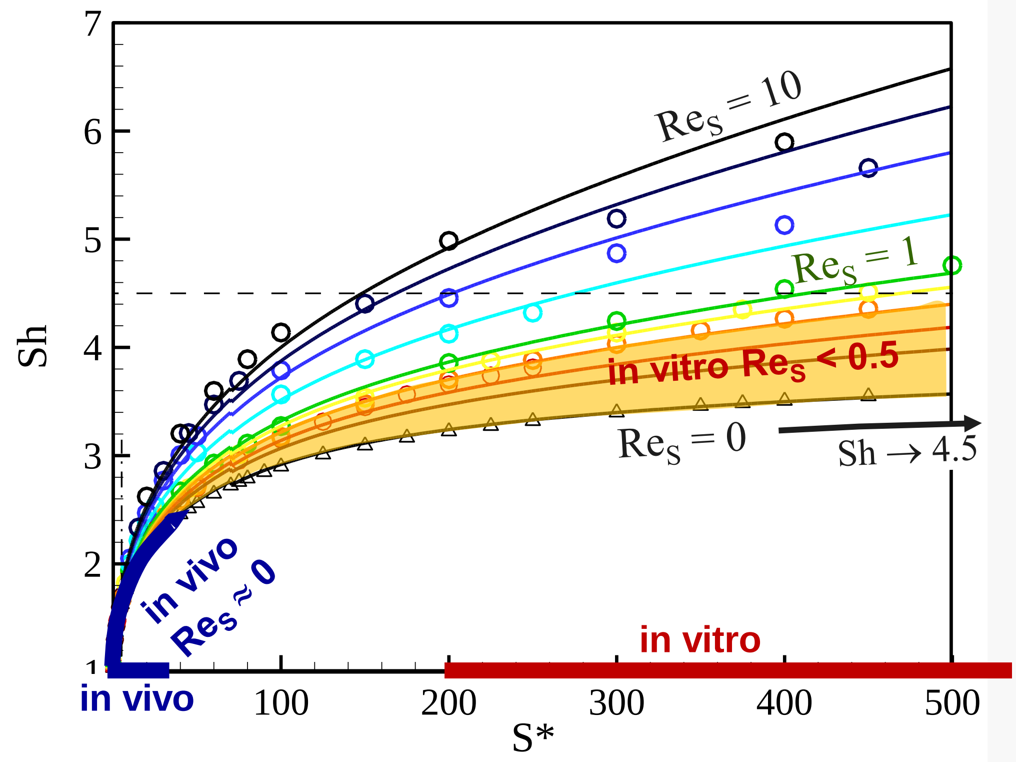
for Felodipine

for D< 100 µm

	Intestine	USP II
Shear Reynolds Number	$Re_S <$ 0.0007 - 0.003	$Re_S <$ 0.25 - 0.5
Shear Peclet Number	$S^* <$ 10 - 25	$S^* <$ 250 - 500

Enhances Dissolution Rate (next)

The Influence of Hydrodynamic Shear on Dissolution



$$\mathbf{Sh} \equiv \frac{\textbf{surface flux}}{D_m (C_s - C_b)/R}$$

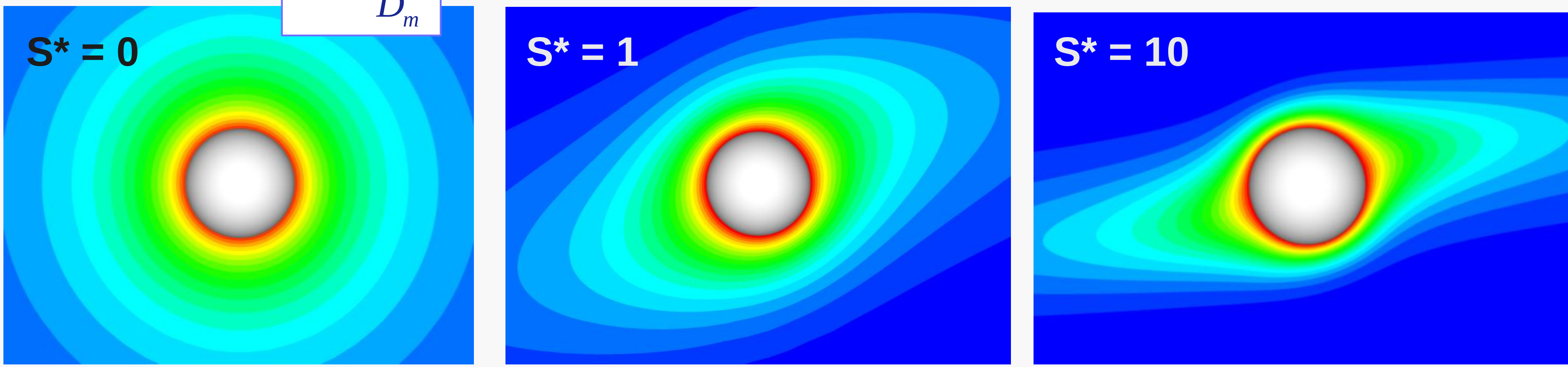
Shear Reynolds number: $Re_S = \frac{SR^2}{\nu}$

Shear Peclet Number: $S^* = \frac{SR^2}{D_m}$

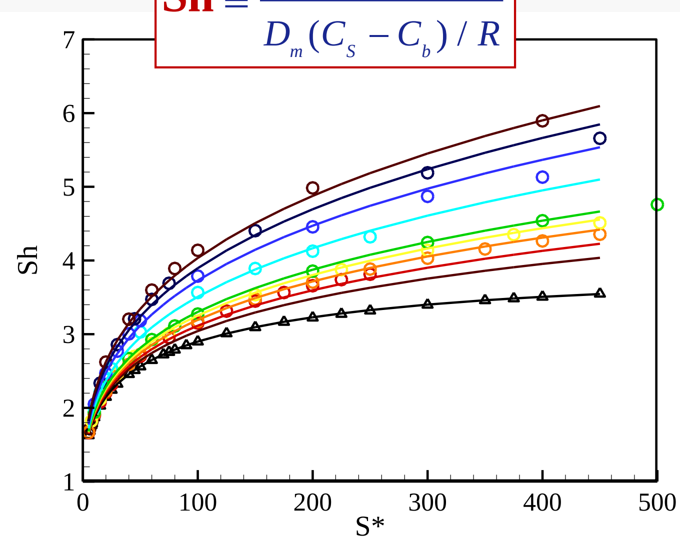
- **Shear increases dissolution rate in intestine:** $\frac{\mathbf{dC_b}}{\mathbf{dt}} = \frac{D_m}{V_b}\left[C_S - C_b(t)\right] R_{eff}(t)\,\mathbf{Sh(t)}$
- **Enhancement is 2-3 times larger in the USP II device compared to the intestine**

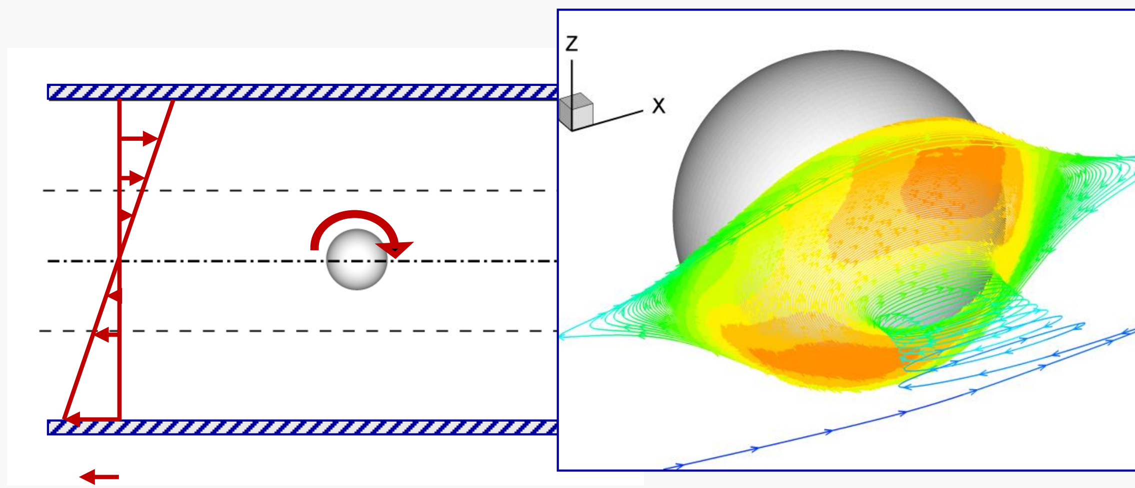
Why Hydrodynamic Shear Enhances Dissolution Rate

$$S^* = \frac{SR^2}{D_m}$$



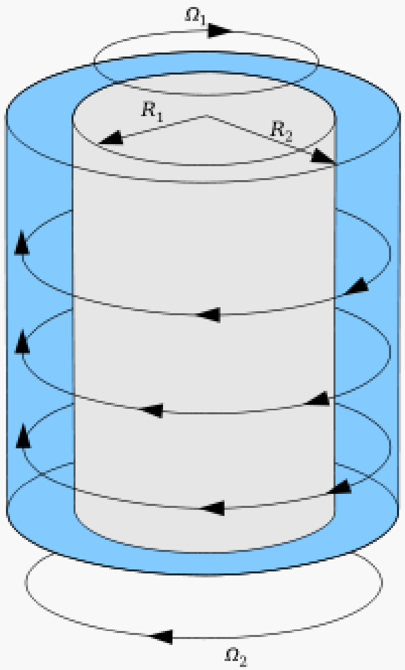
$$\mathbf{Sh} \equiv \frac{\textbf{surface flux}}{D_m (C_s - C_b) / R}$$

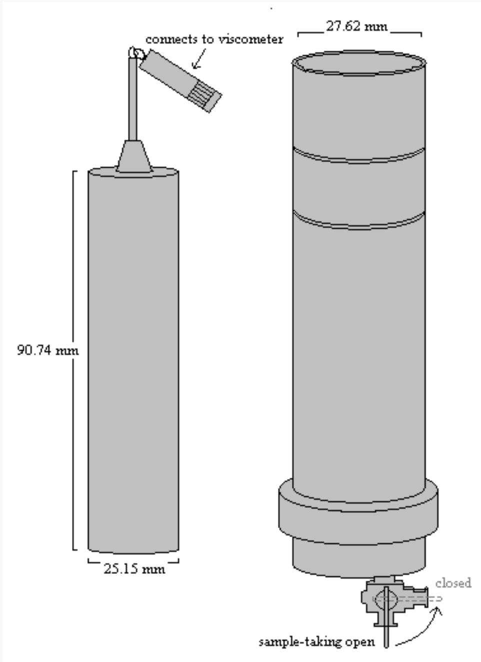




Validation with Coutte Cell In Vitro Shear Experiments:

(Deanna Mudie, Greg Amidon)





3 Initial Particle Distributions

$R_{avg,\upsilon}$: $R_1 = 26\mu m,\ R_2 = 50\mu m,\ R_3 = 71\mu m$

3 Rotation Rates

RPM	Shear Rate (S)
0.5	$0.532/s$ (*in vivo* relevent)
10	$10.6/s$ (*in vivo* relevent)
100	$106/s$ (*in vitro* relevent)

Benzoic Acid

$\upsilon_m = 92.73\ \text{cm}^3/\text{mole}$

$C_S = 3149\ \mu M = 385\ \mu g/ml$

$C_S\upsilon_m = 2.92\times10^{-4}$ □ 1

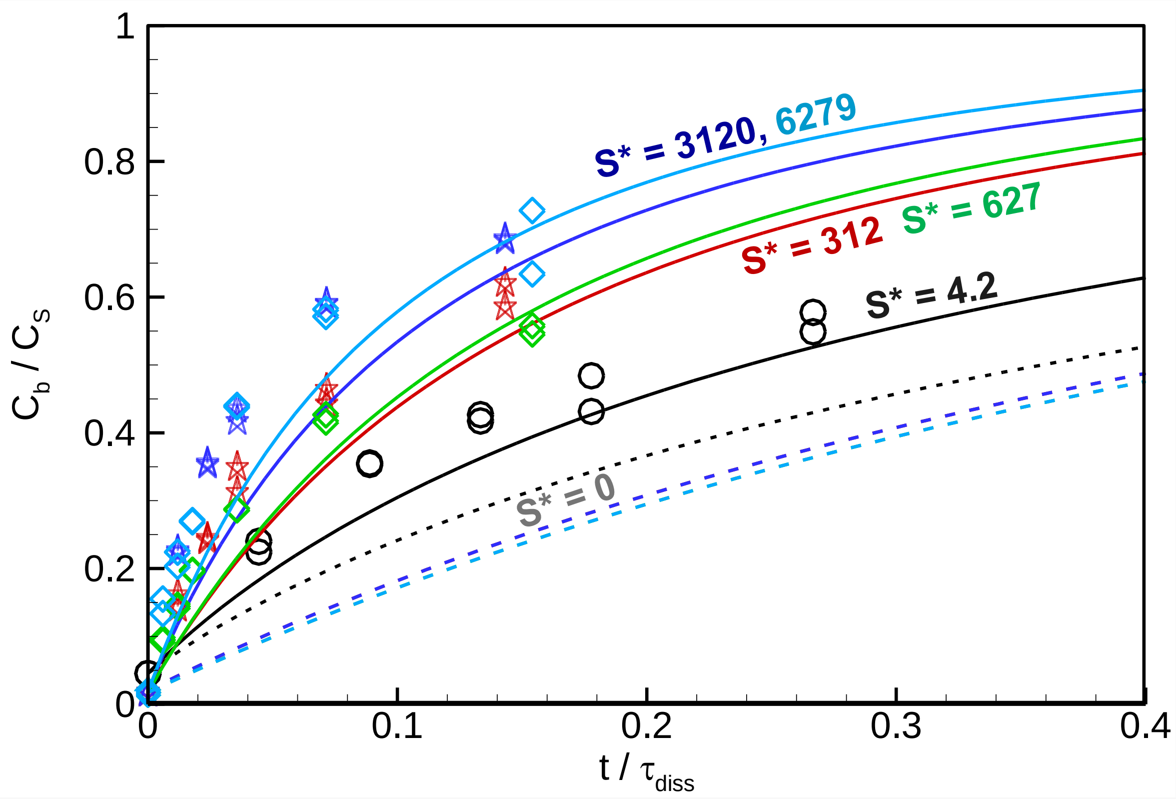
$D_m = 8.47\times10^{-7}\ cm^2/s$

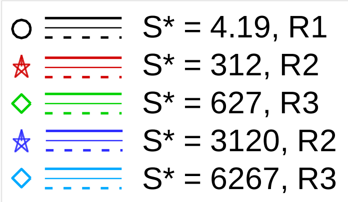
$C_{tot} = 417\mu g/ml \Rightarrow C_{tot}/C_S = 1.08$

$\Rightarrow C_{tot}\upsilon_m = V_0/V_C = 3.15\times10^{-4}$ □ 1

RPM	$(R_{v,avg})_0$	S* for $(R_{v,avg})_0$	S* for $(R_{max})_0$
0.5	26 mm	4.19	20
10	50 mm	312	700
10	71 mm	627	1100
100	50 mm	3121	7000
100	71 mm	6270	11000

Validation of the "Hierarchical Polydisperse Mathematical Model"





Shear Peclet Number

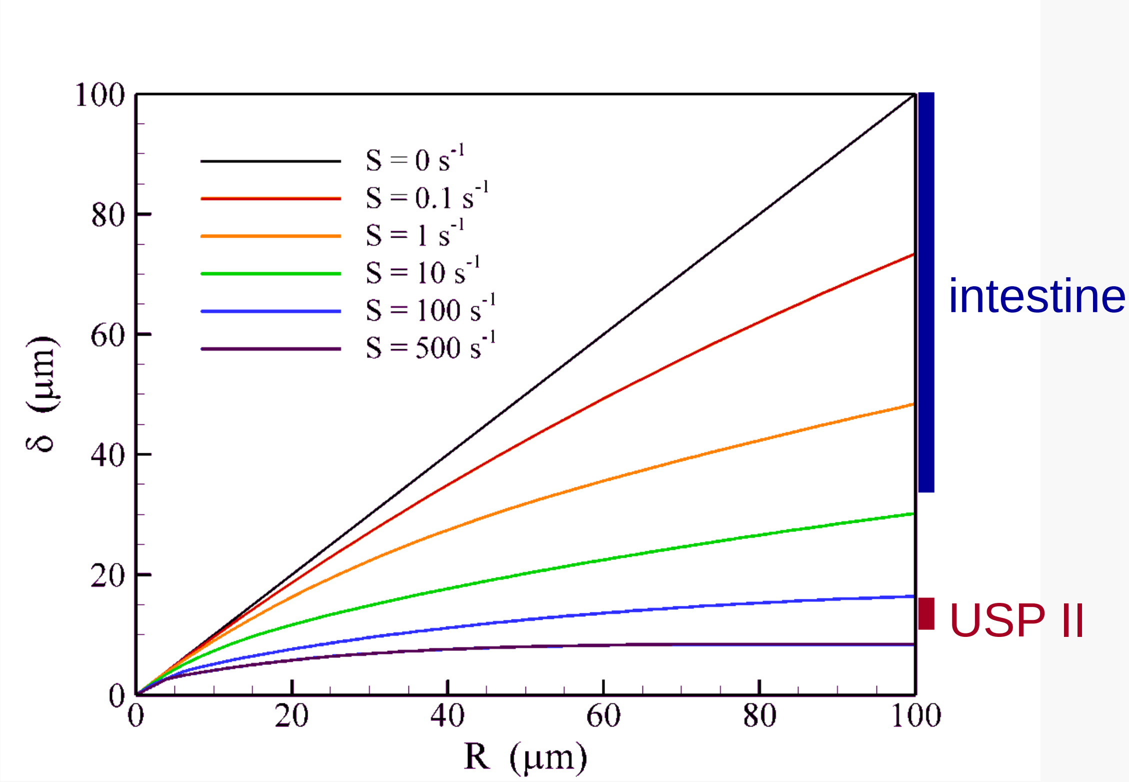
$$S^* = \frac{SR^2}{D_m}$$

$$\frac{dR_j(t)}{dt} = -\upsilon_m D_m \frac{[C_S - C_{b,j}(t)]}{R_j(t)} Sh_j(t)$$

$$Sh_j = 1 + \Delta_{confinement} + \Delta_{shear}$$

Effect of Shear on Diffusion Layer Thickness Commonly used in Mathematical Models

$$\frac{dR_j}{dt} = -\upsilon_m D_m \frac{[C_S - C_{b,j}]}{\delta_j}$$



Effect of Hydrodynamic Shear (and convection) on diffusion layer thickness δ:

1. reduce the thickness of the diffusion layer δ
2. reduce δ more at larger particle sizes

Conclusion

Hydrodynamic Influences are Important to Drug Release and Distinctions between *In Vivo* and *In Vitro* Dissolution Dynamics,

and therefore need to be understood, characterized and properly incorporated into mathematical and in vitro modeling.