Impact of drug incorporation into micelle on reduced griseofulvin and meloxicam permeation across a hollow fiber membrane

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NEXT-GENERATION DELIVERY INNOVATIONS

Why Study Combined Dissolution-Permeation?

- Overall goal: Develop a dissolution-HFM system
- Orally administered drugs (i.e., poorly soluble drugs)
  - Dissolution and Permeation
- Permeation is required for dissolution of poorly soluble drugs
  - Permeation allows for subsequent, additional drug dissolution
- Drug micellization can reduce drug permeation (in vitro)

Reduced permeability with micelle Yano et al.

- **Model Drugs** : Griseofulvin and Troglitazone
- **Media:** Sodium Taurocholate
- **Membrane:** CaCo2 and Dialysis membranes (MW cutoff 1000 Da)
- **Set up:** Side by side chamber (1.77 cm^2 area)
- **Assumption:** Permeation from only free drug

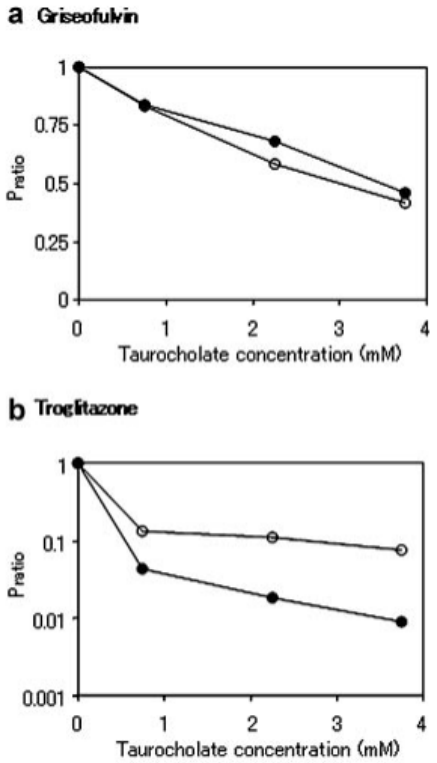


Fig. Effect of ST conc on griseofulvin (a) and troglitazone in D/P system. open circle (CaCo2 monolayer), closed circle dialysis membrane)

Ref- Yano et al. 2009

Reduced permeability with micelle Fisher et al.

- **Model Drugs :** Ketoprofen and Nadolol
- **Media:** Poloxamer 188
- **Membrane:** Phospholipid vesicle-based permeation barrier
- **Set up:** Ultrafiltration using Transwell (10kD)
- **Assumption:** Permeation from only free drug

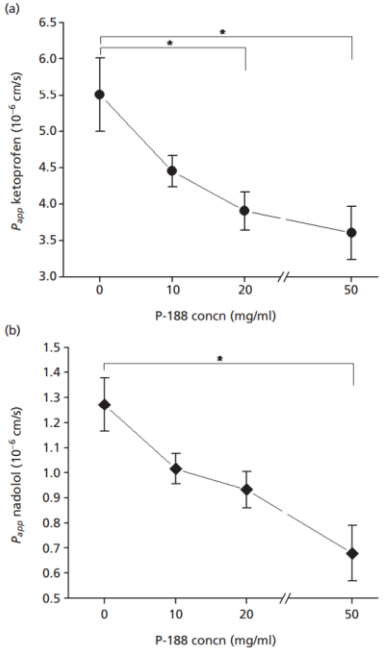


Fig. Effect of P-188 on permeation of ketoprofen (a) and nadolol (b)

Ref- Fisher et al. 2011

Improved permeability with colloid shuttling Narula et al.

- **Model Drug** : Atazanavir
- **Media:** Phosphate buffer with hydroxypropyl methylcellulose acetate succinate (HPMCAS)
- **Membrane:** Polyvinylidenefluoride (PVDF)
- **Set up:** Franz diffusion cells
- **Assumption:** Permeation from free drug, enhanced permeation from colloid shuttling

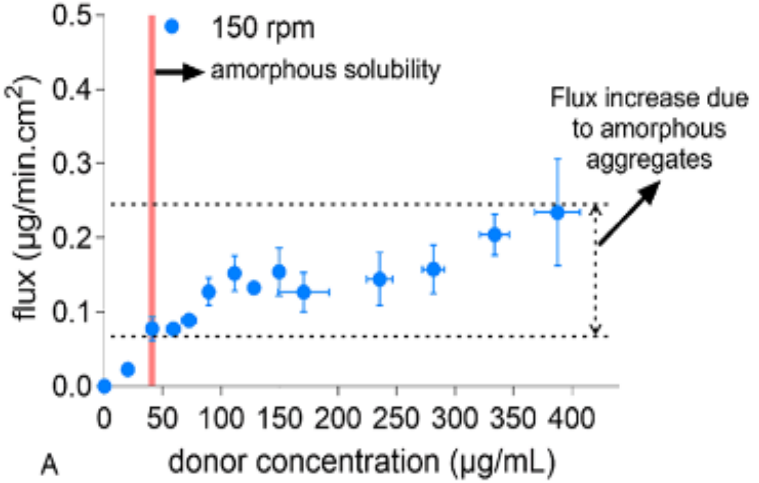


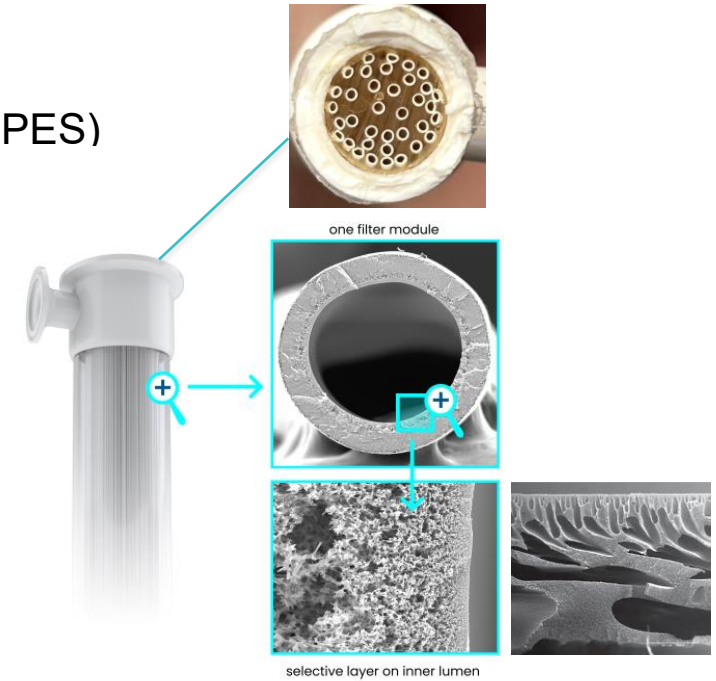
Fig. Higher diffusion flux of atazanavir with amorphous aggregates

Ref- Narula et al. 2022

D-HFM apparatus

mPES membrane and liquid flow

- **Material:** Hydrophilic modified polyether sulphone (mPES)
- **Total hollow fibers**: 36
- **High surface area**: 115 cm^2
- **Molecular weight cut off**: 10kD
- **Nominal pore size**: 2.5 nm diameter
- **Length**: 20cm
- **Area/volume**: at least 0.128 /cm
- **Flow**: Continuous laminar flow

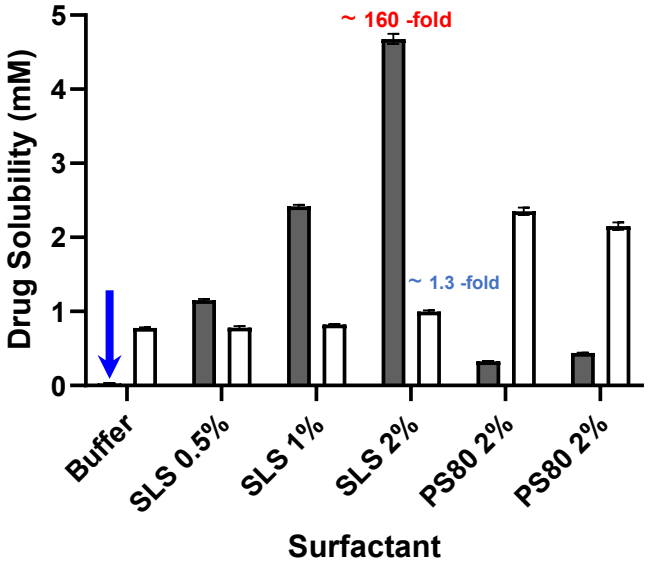


Microscopic view of selective layer for permeation

Objectives

- Focus on Permeation component of D-HFM
- To assess the impact of micellization on drug permeation across HFM
  - **Model Drugs**: Griseofulvin, Meloxicam
  - **Surfactants**: Sodium Lauryl sulfate (SLS), Polysorbate 80 (PS80), Polyoxyethylene (10) lauryl ether (POE10)
- Three competing models for drug permeation
  - Permeation from only free drug
  - Permeation from micelle bound drug and free drug
  - Permeation from only free drug, but enhancement via micelle shuttling

Effect of Surfactant on Drug Solubility



Griseofulvin
Meloxicam

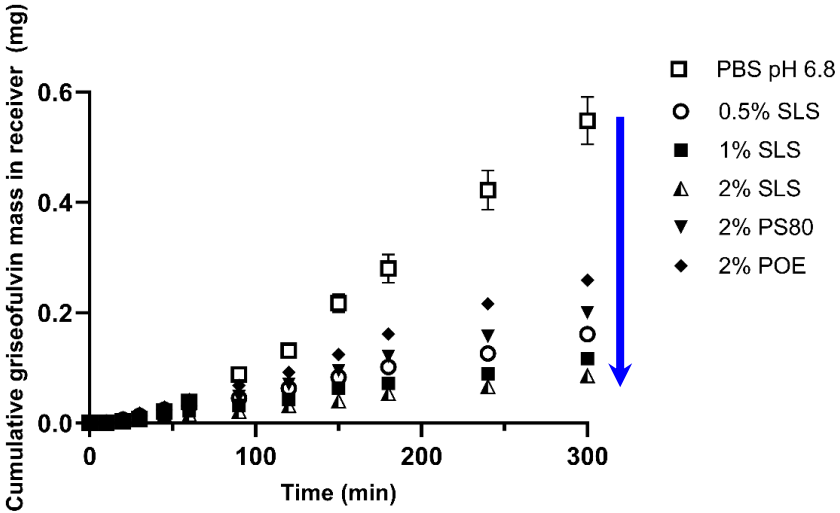
HFM studies were conducted under unsaturated drug conditions

Griseofulvin solubility without surfactant = 0.029mM

Griseofulvin was micelle incorporated to a greater extent than meloxicam.

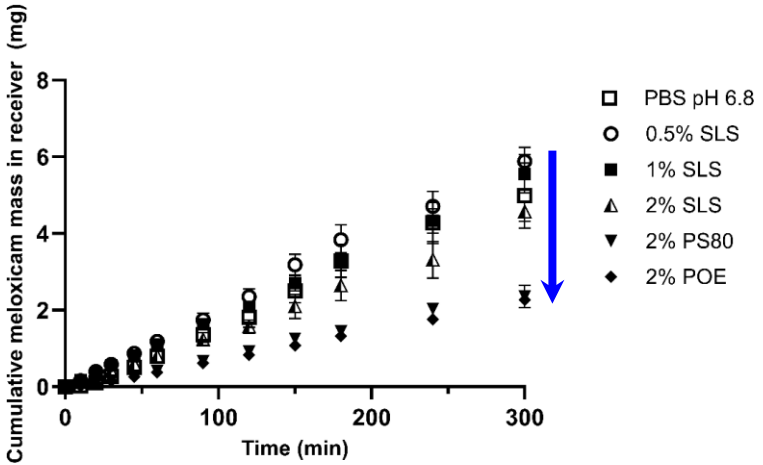
Effect of Surfactant on mass transfer across HFM

Griseofulvin 6µg/ml donor concentration



2% SLS, PS80, and POE griseofulvin flux reduced by 10, 3 and 3-fold

Meloxicam 60µg/ml donor concentration



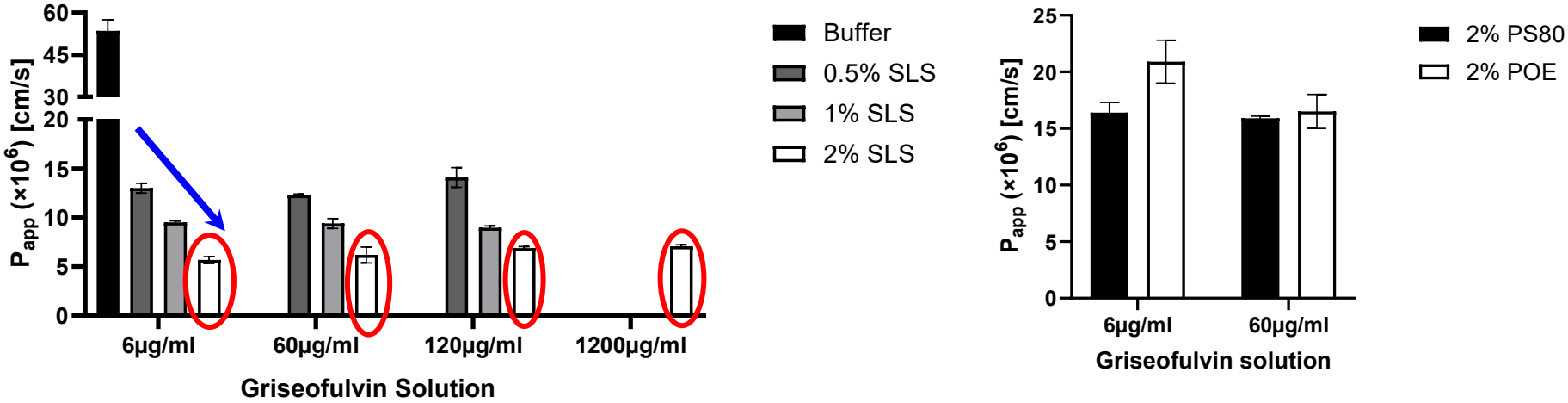
2% SLS, PS80, and POE meloxicam flux by 1.3, 2 and 2.5-fold

Permeability data of Griseofulvin

Griseofulvin concentration (µg/ml)	Media	P_{app} (×10⁶) [cm/s] using simple flux model and receiver data	P_{app} (×10⁶) [cm/s] using simple flux model and donor data
6	No surfactant	53.6±3.9	86.3±4.6
	SLS 0.5%	13.0±0.5	22.8±1.96
	SLS 1%	9.50±0.16	18.1±0.9
	SLS 2%	5.67±0.35	3.61±1.60
	PS80 2%	16.4±0.9	9.50±3.40
	POE 2%	20.9±1.9	16.01±4.69
60	SLS 0.5%	12.3±0.1	20.3±2.59
	SLS 1%	9.4±0.5	16.6±4.10
	SLS 2%	6.18±0.82	10.02±3.02
	PS80 2%	15.9±0.2	26.5±6.8
	POE 2%	16.5±1.5	17.8±0.67
120	SLS 0.5%	14.1±1.0	11.8±3.64
	SLS 1%	8.96±0.19	23.7±2.2
	SLS 2%	6.88±0.16	8.13±1.08
1200	SLS 2%	7.06±0.15	12.6±4.11

$$J = P_{app} \times C$$

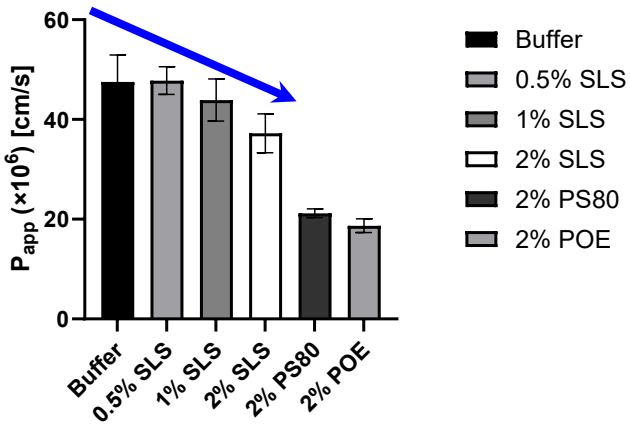
Impact of Surfactant on Griseofulvin P_{app}



Rank order 2% SLS < 1% SLS < 0.5% SLS < 2% PS80 < 2% POE < Buffer

Impact of Surfactant on Meloxicam P_{app}

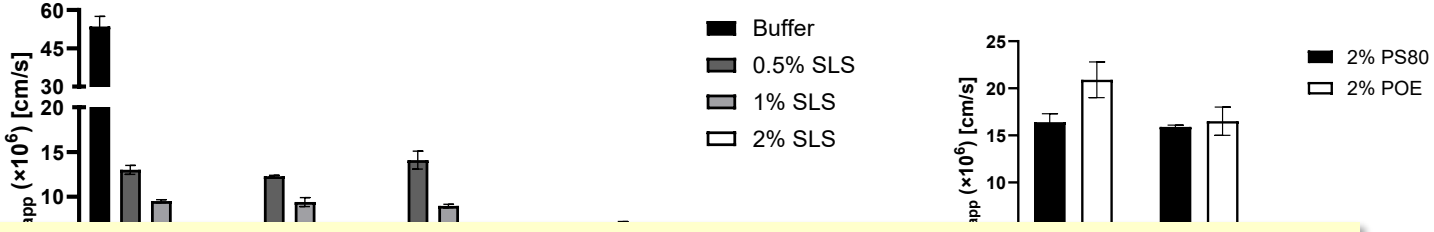
Meloxicam concentration (µg/ml)	Media	P_{app} ($\times 10^6$) [cm/s] using simple flux model and receiver data	P_{app} ($\times 10^6$) [cm/s] using simple flux model and donor data
60	No surfactant	47.5±5.4	59.2±3.7
	SLS 0.5%	47.8±2.8	63.1±0.1
	SLS 1%	43.9±4.2	57.2±9.1
	SLS 2%	37.2±3.9	53.8±0.1
	PS80 2%	21.2±0.9	15.7±3.1
	POE 2%	18.7±1.4	16.1±3.9



Rank order 2% PS80 = 2% POE < 2% SLS < 1% SLS < 0.5% SLS = No surfactant

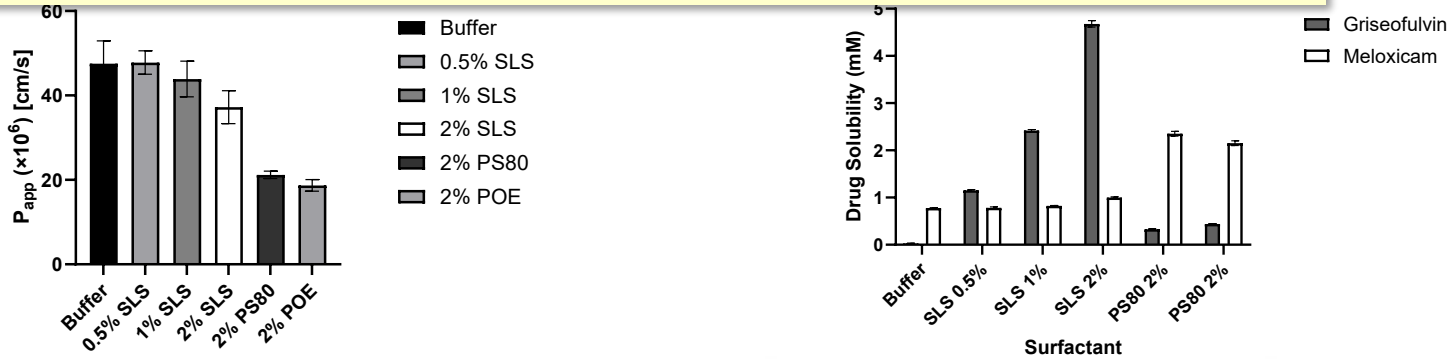
Relationship between free drug conc and permeability

Griseofulvin Solution



Griseofulvin was micelle incorporated to a greater extent than meloxicam, such that griseofulvin flux decreased to a greater extent than for meloxicam

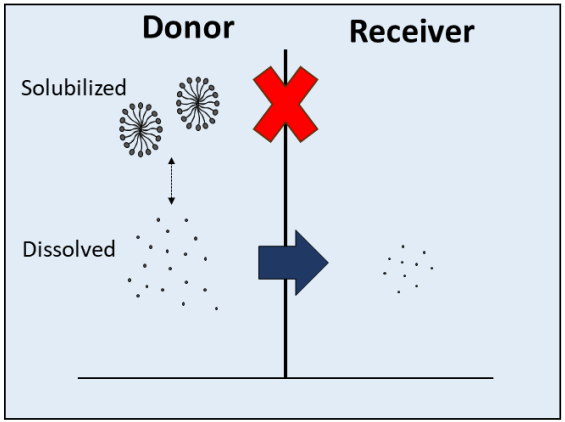
Meloxicam Solution 60µg/ml



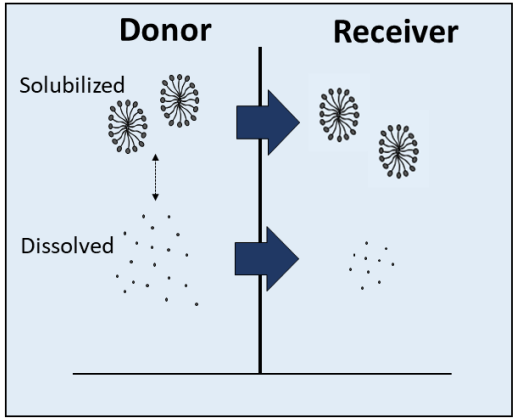
Drug permeation model

Three different mechanism for Drug Permeation in presence of surfactant

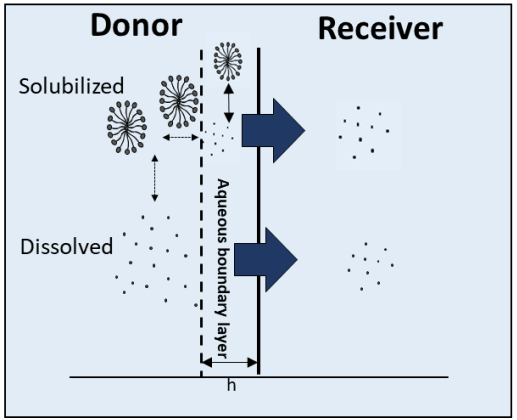
1. Free drug only



2. Free + Micelle bound drug



3. Free drug, but enhancement via micelle shuttling



Calculation of free drug conc

Total Micelle Sites model

- Need to calculate free drug concentration (since HFM studies were below drug saturation)
- Calculation based on equilibrium between free drug, total micelle sites, and loaded micelle sites (as determined from solubility studies).

$$C_f^m + M_t \leftrightharpoons C_b$$

- The equilibrium coefficient K_t of this mass action is:

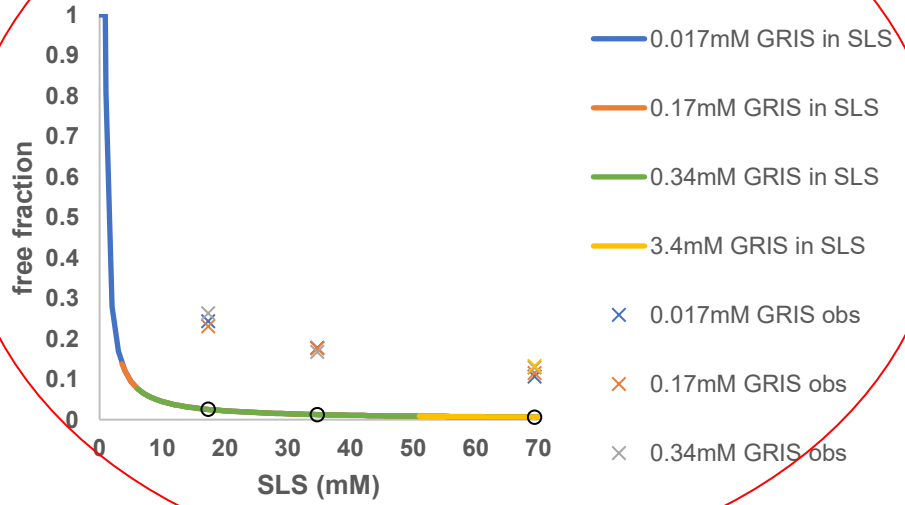
$$K_t = \frac{C_b}{C_f^m M_t}$$

Drug Free fraction with surfactant

$$K_t = \frac{C_b}{C_f^m M_t}$$

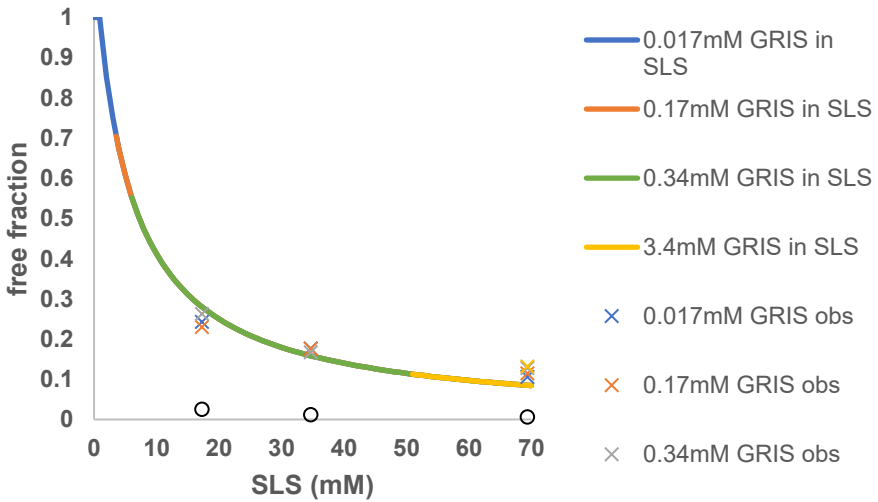
From Solubility studies

$K_t = 34.5 mM^{-1}$



From HFM studies

$K_t = 2.31 mM^{-1}$



Permeation model from only free drug: Griseofulvin

1. Free drug only

Media	Estimated free fraction	Fold reduction in free fraction compared to surfactant free	Fold reduction in observed apparent griseofulvin P_{app} compared to surfactant free (6 µg/ml HFM study)	Discrepancy in permeation model from only free drug
SLS 0.5%	0.0253	39.6	4.12±0.17	9.60-fold low
SLS 1%	0.0120	80.2	5.64±0.35	14.2-fold low
SLS 2%	0.00622	161	9.45±0.18	17.0-fold low
PS80 2%	0.0884	11.3	3.26±0.31	3.46-fold low
POE 2%	0.0663	15.1	2.56±0.40	5.89-fold low

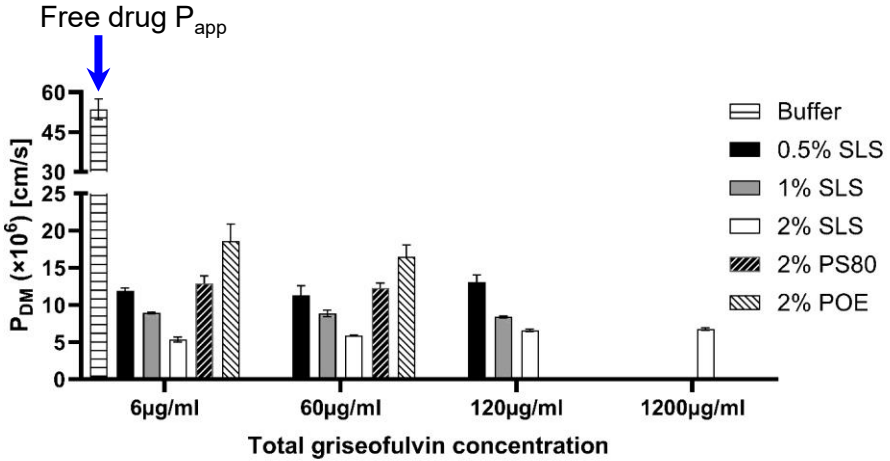
Why this discrepancy?

5-20 times higher free drug across HFM than supported by solubility studies

Permeation model permeation from both free drug and micelle-bound drug: Griseofulvin

2. Free + Micelle bound drug

$$P_{DM} = \frac{J_t - J_f^m}{C_b}$$



Drug-containing micelle permeability (P_{DM}) for griseofulvin in the presence of surfactant

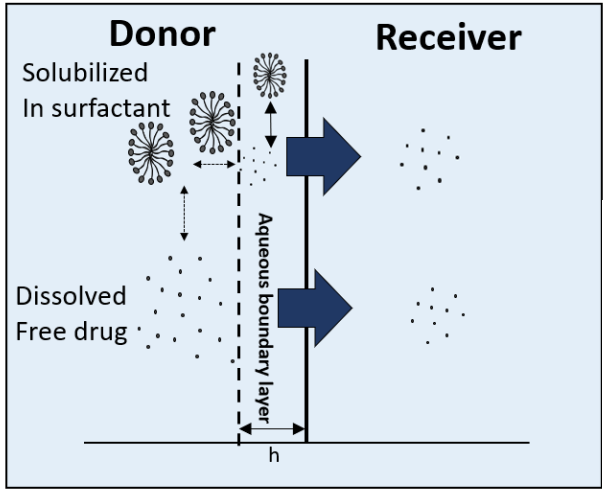
P_{DM} is the permeability of drug-containing micelles
J_t total absorptive drug flux from the donor compartment into the receiver compartment, J_f^m is the absorptive drug flux of free drug in the presence of surfactant

"Nominal" pore size: ~2.5 nm diameter

SLS micelle: ~3.9 nm diameter

Permeation with enhancement from micelle shuttling

3. Free drug, but enhancement via micelle shuttling

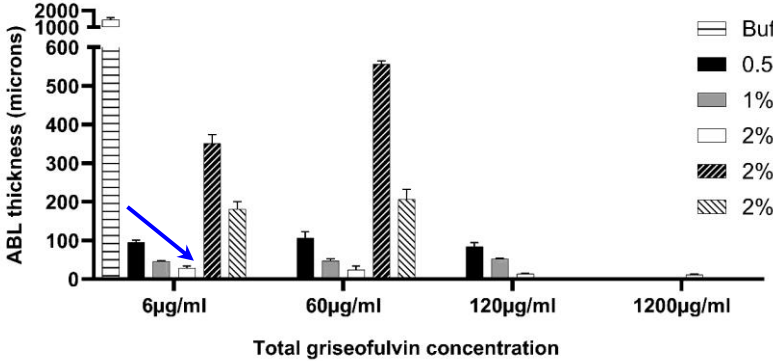


For barriers in series (i.e., a single ABL and a membrane)

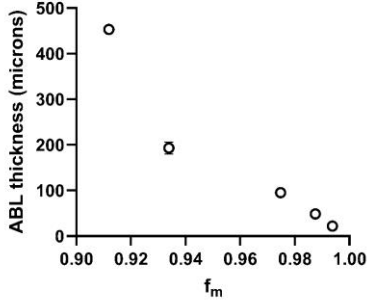
$$\frac{1}{P_f} = \frac{1}{P_f^{abl}} + \frac{1}{P_f^{mem}}$$

D_f is a free drug diffusivity, and h is aqueous boundary layer thickness

$$P_f^{abl} = \frac{D_f}{h}$$ With and without surfactant



Calculated nominal aqueous boundary layer (ABL) thickness of HFM



ABL thickness vs fraction micelle bound

Conclusions

- Reduced Griseofulvin and meloxicam permeation across HFM due to drug incorporation into micelle
  - Surfactants (i.e., SLS, PS80, POE)
- Permeation models were assessed

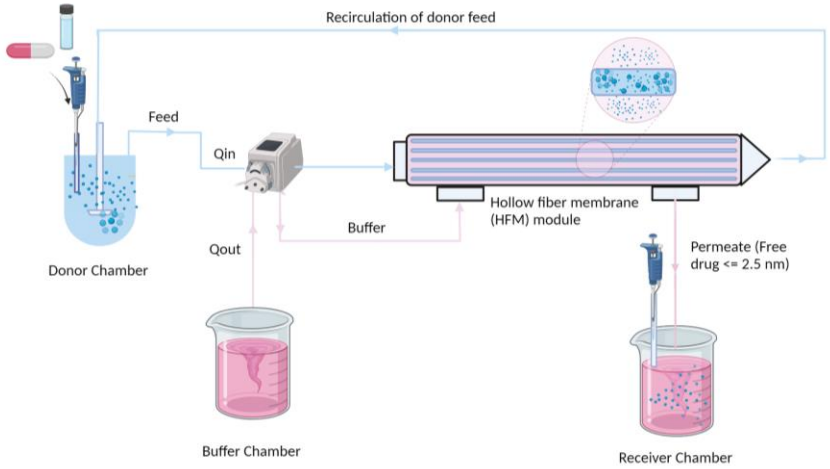

- Only free drug


- Permeation from free drug + micelle bound drug


- Free drug + enhanced permeability from micelle shuttling

Implications: Dissolution-Permeation Understanding

- Overall goal: Develop a dissolution-HFM system, especially for poorly soluble drugs.
- Need to understand drug permeation in the presence of surfactant micelles
  - Micellar entrapment
  - Negative food effect



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Me operating UPLC