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Predicting surfactant effects on drug permeation across hollow fiber membrane

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ABSTRACT

The hollow fiber membrane (HFM) system is a potential combined dissolution/permeation in vitro tool to predict oral solid dosage form performance. However, drug permeability interpretation in the presence of surfactants remains mechanistically challenging, particularly when surfactants are present in both the donor and receiver compartments. A model denoted the reduced resistance model was recently employed to explain enhanced drug permeability when surfactant was present in the receiver. The objective was to re-examine previously published HFM flux of griseofulvin and meloxicam to consider the reduced resistance model as an additional contributing mechanism impacting drug flux. Published HFM data under all four surfactant experimental scenarios (i.e., no surfactant, surfactant in the receiver only, surfactant in the donor only, and surfactant in both donor and receiver) were re-analyzed. For the latter two most complex scenarios, there were six competing permeation models. For these two scenarios, the best predictive model for griseofulvin was the reduced resistance model for total donor drug concentration; meanwhile, for meloxicam, which was much less micelle incorporated, the best predictive model was the simple free drug permeation model. Overall, these findings demonstrate that drug permeation across HFM in surfactant-containing systems is governed by the interplay between donor-side micellar sequestration and receiver-side resistance reduction.

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Introduction

The hollow fiber membrane (HFM) has emerged as a potential dissolution/permeation in vitro tool for elucidating oral drug product performance.[1–4] HFM provides a relatively high surface area-to-volume ratio, thereby partially mitigating the limitations of very low permeation rates.

The impact of receiver-side solubilizers on drug transport has been explored across various experimental setups, in part through maintaining sink conditions and/or high mass balance. Recently, Murray et al. identified a reduced resistance model to explain HFM flux data where solubilizing receiver additives (i.e., surfactants, cyclodextrins, and bovine serum albumin) increased drug flux by lowering the diffusional resistance within both the membrane and the receiver-side boundary layer of HFM.[4] For example, by testing griseofulvin with nine receiver additives it was demonstrated that flux enhancement followed the rank-order of the receiver-to-donor media solubility ratio. Mechanistically, this was attributed to a reduction in receiver-side resistance, leaving the donor-side boundary layer as the primary rate-limiting step, and hence increasing griseofulvin apparent permeability. The membrane resistance also appeared to be reduced, likely due to the presence of the receiver media additives in the membrane pores. For this experimental scenario, the reduced resistance model considers the chemical potential gradient, rather than the simple concentration gradient, to be the true driving force for diffusion. It employs the solubility difference between surfactant-containing media and additive-free media as an experimentally accessible approximation of the chemical potential gradient.

In another prior HFM study, griseofulvin apparent permeability (P_{app}) was 53.6×10^{-6} cm/s with no surfactant present in either donor or receiver [denoted scenario A].[3] With 2% sodium lauryl sulfate (SLS) in the receiver only [denoted scenario B], P_{app} increased to 146×10^{-6} cm/s. In contrast, with 2% SLS in the donor only [denoted scenario C], P_{app} dropped to 0.708×10^{-6} cm/s. With 2% SLS in both the donor and receiver [denoted scenario D], P_{app} decreased to 6.28×10^{-6} cm/s, which was in between P_{app}'s observed from scenarios B and C.

The present work revisits this HFM data, as well as that of meloxicam, with three surfactants [sodium lauryl sulfate (SLS), polysorbate 80 (PS80), and polyoxyethylene 10 lauryl ether (POE10)] under

Abbreviations: HFM, Hollow fiber membrane; SLS, sodium lauryl sulfate; PS80, polysorbate 80; POE10, polyoxyethylene 10 lauryl ether.

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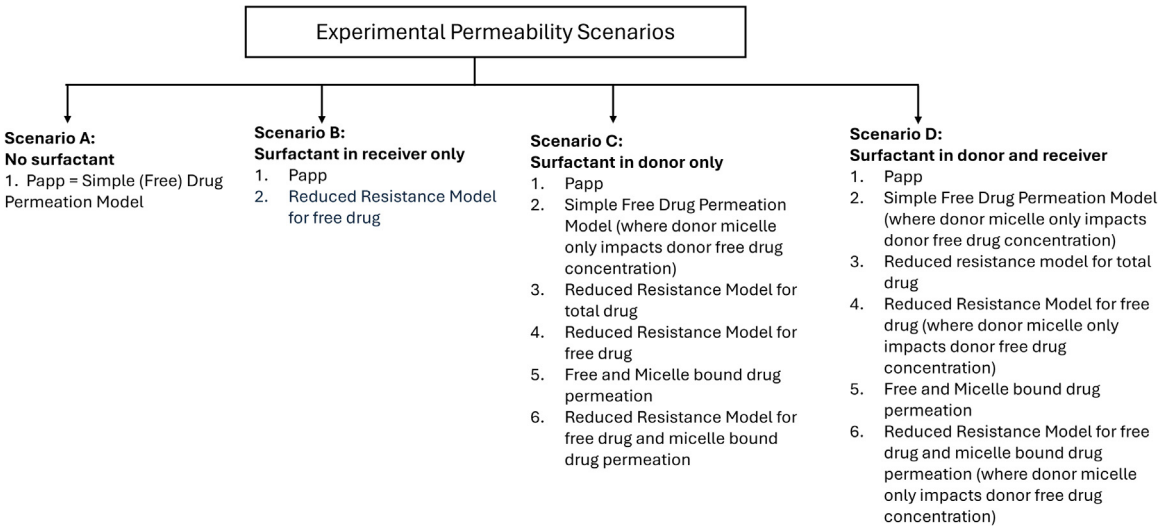


Fig. 1. Workflow to predict permeability in presence and absence of surfactant micelles. Four different scenarios were analyzed with competing models to elucidate the mechanism of drug permeability across HFM. Scenario B involved surfactant in receiver only. Scenario C involved surfactant in donor only. Scenario D involved surfactant in both donor and receiver. The same six competing models were considered for scenario C and D. Each scenario C and D, same six competing models were considered. Model C5 is model C2 with micellular permeability component. Model C6 is model C4 with micellular permeability component. Model D5 is model D2 with micellular permeability component. Model D6 is model D4 with micellular permeability component.

unsaturated donor conditions.[3] Griseofulvin extensively partitions into micelles, while meloxicam does not. In particular here, the objective was to consider the reduced resistance model as an additional contributing mechanism impacting drug flux, which was not previously considered. Previously, permeation from both free griseofulvin and micelle-bound griseofulvin successfully accommodated observed flux, where micelle permeability was about 5-fold lower than free drug permeability. As results here show that, for the more complex scenarios C and D, the reduced resistance model for total donor drug concentration was the best predictive model for griseofulvin, while the simple free drug permeation model was best for meloxicam, which was much less micelle incorporated than griseofulvin.

Materials and methods

Data were sourced from previously published HFM permeation experiments.[3] Briefly, griseofulvin and meloxicam permeability was evaluated using a 10 kDa MWCO modified poly(ether sulfone) HFM module (Repligen; Marlborough, MA) with and without surfactant. Experiments were conducted at a co-current flow rate of 2 mL/min for both donor and receiver. Media in the donor circuit was recycled, while only fresh media was passed through on the receiver side to maintain a constant physical sink. Six media types at pH 6.8 were utilized: phosphate buffer with and without surfactant (0.5%−2% SLS, 2% PS80, or 2% POE10). For the purposes of this analysis, only data based on sampling from the receiver-side was considered.

Overall approach

Fig. 1 illustrates the workflow to predict griseofulvin permeability in presence and absence of surfactant. Four different experimental scenarios, denoted A – D, were analyzed with competing models to elucidate the mechanism of drug permeability across HFM. Experimental scenario A concerned studies with no surfactant and in either donor or receiver. Scenario B involved surfactant in receiver only. Scenario C involved surfactant in donor only. Scenario D involved surfactant in both donor and receiver.

Scenario A merely involved calculating apparent permeability P_{app} based on total donor drug concentration and is thus sufficiently described by the simple drug permeation model. Due to no surfactant in donor, all (total) drug is also free drug (i.e., not micelle-bound). Scenario B data was analyzed via both simple P_{app} calculation (model B1), as well as the reduced resistance framework(model B2).

Data from experimental scenarios C and D were subjected to the same six competing models. Model D1 (P_{app} calculation based on total donor drug concentration), D2 (simple free drug permeation model, where donor micelles only impact donor free drug concentration), and D5 (free and micelle-bound drug permeation model) were previously considered.[3] Models D3, D4, and D6 each consider a reduced resistance component, as well as other possible impacts.

Experimental scenarios and competing permeation models

Four experimental scenarios were evaluated based on the presence or absence of surfactant in the donor and/or receiver compartments, in Fig. 1. Table 1 details the differing model elements, including permeation based on free or total drug, a possible reduced resistance effect, and the potential for drug-loaded micelles themselves to cross the membrane. For scenarios B-D, competing permeation models were examined to assess the contribution of total versus free drug, reduced resistance effects on membrane permeability, and possible micelle-bound drug permeability across HFM.

With the benefit of existing experimental evidence supporting the reduced resistance model as the preferred explanation for scenario B, the most complex experimental scenarios were C (surfactant in donor) and D (surfactant in both donor and receiver). A preferred model was identified on the basis of congruence between predicted and observed flux. Of note, the two most simple models, namely the simple drug permeation model and the simple free drug permeation model, did not involve flux prediction, but rather calculated apparent permeability from observed flux and (calculated) donor drug concentration. Thus, these approaches were not strictly predictive.

Scenario A: no surfactant in either donor or receiver

One model was considered. Model A1 is the simple drug permeation model (i.e., drug flux across membrane is only due to permeation of total drug). In the case of Scenario A, the free drug permeation model is equivalent to the total drug permeation model

Table 1
Experimental scenarios and competing models for drug permeation across HFM in the presence or absence of surfactants.

Experimental scenario	Model	Permeation of total or free drug?	Reduced resistance model component?	Micelle permeation allowed?
A	A1	Total (=free)	No	No
B	B1	Total (=free)	No	No
	B2	Total (=free)	Yes	No
C	C1	Total	No	No
	C2	Free	No	No
	C3	Total	Yes	No
	C4	Free	Yes	No
	C5	Free	No	Yes
	C6	Free	Yes	Yes
D	D1	Total	No	No
	D2	Free	No	No
	D3	Total	Yes	No
	D4	Free	Yes	No
	D5	Free	No	Yes
	D6	Free	Yes	Yes

Experimental scenario A involved no surfactant, scenario B involves surfactant only in receiver, scenario C involves surfactant only in donor, and scenario D involves surfactant in both donor and receiver. Differing model elements included permeation based on free or total drug, possible reduced resistance model component, and possible micelle permeation component.

as no drug is micelle-bound. From observed flux, griseofulvin P_{app} was previously calculated to be 53.6×10^{-6} cm/s.[3]

Scenario B: surfactant in receiver only

Two models were considered. Like for scenario A, all (total) donor drug is free. Model B1 is the simple drug permeation model P_{app} was previously calculated to be 146×10^{-6} cm/s for griseofulvin and 72.1×10^{-6} cm/s for meloxicam from observed fluxes in 2% SLS.[3]

Model B2 is the reduced resistance model for total drug.[4] Equation for P_{app} is:

$$\frac{1}{P_{app}} = \frac{1}{P_d} + \frac{1}{HP_m} + \frac{1}{HP_r} \quad (1)$$

where P_d, P_m, and P_r are the individual donor-side, membrane, and receiver-side permeabilities and H is the ratio of the drug solubility in the presence of surfactant versus the drug solubility in absence of surfactant. Hence, $H > 1$. Here, H is also equal to the ratio of the drug solubility in receiver versus the drug solubility in donor.

From Murray et al., the resistances associated with P_d, P_m, and P_r contributed 27.72%, 18.30%, and 53.98% to total permeation resistance. Without surfactant, P_{app} of griseofulvin was 35.6×10^{-6} cm/s. Hence, here, P_d, P_m, and P_r were taken to be 193×10^{-6} cm/s, 293×10^{-6} cm/s, and 99.3×10^{-6} cm/s, given griseofulvin P_{app} of 53.6×10^{-6} cm/s. That is, the previously reported HFM reduced resistance model was adopted (i.e., same relative contributions of donor, membrane, and receiver barriers), with proportionate scaling due to the slightly higher P_{app} value considered in the current work.

When surfactants were added on the receiver side (scenario B), only increases in flux were observed (i.e., reduced resistance to drug flux). Conversely, only decreases in drug permeation were observed when surfactant was added to the donor only (scenario C) (i.e., increased resistance in donor to drug flux). Likewise, surfactant in both donor and receiver (scenario D) decreased drug permeation (i.e., increased resistance in donor to drug flux, and reduced resistance to drug flux in membrane and receiver).

Of note, the same HFM membrane and experimental conditions (e.g., 2ml/min for donor and receiver flow rates) were employed across Murray et al. and Patel et al.. In similar HFM permeation studies without solubilizing agents, P_{app} tends to be about $35 - 70 \times 10^{-6}$ cm/s.[2–4] This is reflective of the permissive nature of the HFM membrane and its major appreciation as an efficient absorptive sink.

From Eq. (1) and total drug concentration, total drug flux across HFM was predicted and compared to observed flux.

Scenario C: surfactant in donor only

Six models were considered (Fig. 1 and Table 1). Briefly, models C1 and C3 consider total donor drug concentration, while the other four consider free drug concentration. Models C3, C4, and C6 consider a reduced resistance model component to drug permeation. Additionally, models C5 and C6 allow for drug-bound micelles to permeate from donor to receiver.

Model C1 is the simple drug permeation model (i.e., drug flux across membrane is only due to permeation of total drug). Of note here in C1, all (total) donor drug is considered for the donor concentration, although free drug is less than total drug. From observed flux, P_{app} was previously calculated to be 0.708×10^{-6} cm/s for griseofulvin in 2% SLS.[3]

Model C2 is the free drug permeation model (i.e., drug flux across membrane is only due to permeation of free drug). That is, only free donor drug is considered for the donor concentration. Free drug concertation (C_f^m) was calculated as described below. Free drug permeability (P_f) was taken to be 53.6×10^{-6} cm/s for griseofulvin and 47.5×10^{-6} cm/s for meloxicam (i.e., observed P_{app} in the absence of surfactant, scenario A). Flux was predicted from P_f and C_f^m:

$$J_t = P_f \; C_f^m \quad (2)$$

where J_t is the total absorptive drug flux from the donor compartment into the receiver compartment, and C_f^m is the free drug concentration in presence of surfactant.

Model C3 is the reduced resistance model for total drug. Of note for C3, permeability value decreases since the model considers so-called reduced resistance effect (in donor) on drug permeability; all (total) donor drug is considered for the donor concentration, although free drug is less than total drug.

Equation for P_{app} is:

$$\frac{1}{P_{app}} = \frac{H}{P_d} + \frac{1}{P_m} + \frac{1}{P_r} \quad (3)$$

where P_d, P_m, and P_r, are the same as in Eq. (1). H is also the same, in that H is the ratio of the drug solubility in the presence of surfactant versus the drug solubility in absence of surfactant. Hence, $H > 1$. Here, H is also equal to the ratio of the drug solubility in donor versus the drug solubility in receiver, reflecting the presence of surfactant in the donor and not the receiver. Importantly, the donor-side resistance is multiplied by H as an experimentally accessible and interpretable method to reflect the reduced chemical potential of the drug in the donor. It is not intended, however, to describe changes in the boundary layer thickness or diffusivity of the drug in the donor-side boundary layer.

Flux was predicted from P_{app} and total drug donor concentration C_t:

$$J_t = P_{app} \; C_t \quad (4)$$

Of note, Eq. (1) when surfactant in receiver and Eq. (3) when surfactant in donor differ, although each are denoted to be the reduced resistance model. Permeability in Model B2 is favorable by surfactant being present in receiver (only). Permeability in Model C3 is disfavorable by surfactant being present in donor (only). In both cases, surfactant effect is taken to be mediated by modulating the associated membrane component(s). For surfactant in receiver in B2, the resistances associated with the membrane and the receiver boundary layer are reduced. For surfactant in donor in C3, the resistance associated with the donor boundary layer is increased.

A direct alternative to model C3 where permeability is modulated is to only consider free drug in donor (model C2).

Model C4 is the reduced resistance model for free drug. This is similar to model C2, but also considers reduced resistance effect (in donor) on drug permeability. Of note here in C4, permeability value decreases since the model considers reduced resistance effect (in donor) on drug permeability; only free donor drug is considered for the donor concentrations.

Equation for P_{app} is essentially Eq. (3), although only free drug is considered permeable, such that

$$\frac{1}{P_f} = \frac{H}{P_d} + \frac{1}{P_m} + \frac{1}{P_r} \tag{5}$$

Flux was predicted from P_f and C_f^m (Eq. (2)).

Model C5 is the free and micelle-bound drug permeation model (i.e., drug flux across membrane is due to permeation of free drug, and due to permeation of drug-containing micelles). This is model C2, but also considers micelle permeability, which as calculated from:

$$P_{DM} = \frac{J_t - J_f^m}{C_b} \tag{6}$$

where P_{DM} is the permeability of drug-containing micelles, in the presence of surfactant; J_t is the 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 (or micelles); and C_b is concentration of micelle-bound drug (i.e., drug concentration that is micelle-bound per total volume and not per micelle volume). J_f^m was calculated using $P_f = 53.6 \times 10^{-6}$ cm/s. Free drug was calculated per below; C_b is total drug concentration minus free drug concentration.

Model C5 was previously considered in the prior report and was the preferred model for griseofulvin HFM flux.[3]

Since observed total flux was employed to calculate P_{DM}, flux was not predicted, since it would yield back the observed flux. For each drug/surfactant combination, an examination of calculated P_{DM} was employed to assess the suitability of model C5.

Model C6 is the reduced resistance model for free drug and micelle-bound drug permeation model. This is model C4, but also considers micelle permeability, which was calculated from Eq. (6). Of note here in C6, permeability value was decreased, and only free donor drug was considered for non-micellar drug permeation.

Scenario D: surfactant in donor and receiver

Six models were considered (Fig. 1 and Table 1) and were the same as those in scenario C, although surfactant was also present in the receiver.

Model D1 is the simple drug permeation model. From observed flux, P_{app} was previously calculated to be 6.28×10^{-6} cm/s for griseofulvin in 2% SLS.[3]

Model D2 is simple free drug permeation model. Free drug concertation (C_f^m) was calculated as described below. Free drug permeability (P_f) was taken to be 53.6×10^{-6} cm/s from griseofulvin and 47.5×10^{-6} cm/s for meloxicam (i.e., observed P_{app} in the absence of surfactant, scenario A). Flux was predicted using Eq. (2).

Model D3 is the reduced resistance model for total drug. Equation for P_{app} is:

$$\frac{1}{P_{app}} = \frac{H}{P_d} + \frac{1}{HP_m} + \frac{1}{HP_r} \tag{7}$$

where P_d, P_m, and P_r, are the same as in Eq. (1). H is also the same, in that H is the ratio of the drug solubility in the presence of surfactant versus the drug solubility in absence of surfactant. Hence, $H > 1$. Eq. (7) reflects the reduced resistance in the membrane and receiver side due to surfactant in the receiver (Eq. (1)), as well increased resistance on the donor due to surfactant in the donor (Eq. (3)). Again, H serves as a pragmatic method to modify the resistances. The original resistances were calculated by Murray et al. through flow rate experiments with buffer and as such the exact values of the resistances when the system contains only surfactants is not known. This model assumes that resistance is increased on the donor-side (e.g., reduced chemical potential of the drug in the donor and not to describe changes in the boundary layer thickness or diffusivity of the drug in the donor-side boundary layer) and decreased on the membrane and receiver-side.

Flux was predicted from P_{app} and total drug donor concentration C_t using Eq. (4).

Model D4 is the reduced resistance model for free drug. This is model D2, but also considers increased resistance effect (in donor) on drug permeability. Equation for P_{app} is essentially Eq. (7), although only free drug is considered permeable, such that

$$\frac{1}{P_f} = \frac{H}{P_d} + \frac{1}{HP_m} + \frac{1}{HP_r} \tag{8}$$

Flux was predicted from P_f and C_f^m (Eq. (2)).

Model D5 is the free and micelle-bound drug permeation model. This is a similar model to D2, but also allows for micelle permeation across the membrane Of note, this reduced permeability value is calculated from Eq. (6). This model has been applied to this data previously and was preferred prior to the application of the reduced resistance model to drug permeability data.[3]

Model D6 is the reduced resistance model for free drug and micelle-bound drug permeation model. This is similar to model D4, but also considers micelle permeability, which was calculated from Eq. (6). Of note here in D6, permeability value is decreased, and only free donor drug is considered for non-micellar drug permeation.

Free drug concentration in presence of surfactant

Free drug concentration was calculated for various models (i.e., C2, C4, C5, C6, D2, D4, D5, and D6). The previously described Total Micelle Sites Model was used to calculate free drug concertation into each surfactant media.[3] Briefly, equilibrium coefficient (K_t) of drug was calculated from solubility studies and employed to calculate free drug in HFM studies with known total drug donor concentration and known surfactant concentration:

$$K_t = \frac{C_b}{C_f^m} M_t \tag{9}$$

where M_t is concentration of total micelle binding sites (i.e., free and drug occupied) per total volume and not per micelle volume. Values for griseofulvin K_t were 39.2mM^{-1} (for 0.5% SLS), 38.3 mM^{-1} (for 1% SLS), 37.7mM^{-1} (for 2% SLS), 34.7mM^{-1} (for 2% PS80), and 34.8mM^{-1} (for 2% POE10). Values for 1.47mM^{-1} (for 0.5% SLS), 1.29 mM^{-1} (for 1% SLS), 1.31mM^{-1} (for 2% SLS), 1.33mM^{-1} (for 2% PS80), and 1.33 mM^{-1} (for 2% POE10).

Free drug concertation in presence of surfactant was calculated from Patel et al.:[3]

$$C_f^m = \frac{C_t}{1 + K_t\left(\frac{n}{m}([S] - CMC)\right)} \tag{10}$$

where m is aggregation number of surfactant micelle, n is average number of drug molecule per surfactant micelle, [S] is surfactant concentration in media, and CMC is the critical micelle concentration. The equilibrium coefficient is K_t. C_t is total drug concentration.

Values for H and effect of H on apparent permeability

The reduced resistance model is employed in model B2, C3, C4, C6, D3, D4, and D6. Forms of the reduced resistance model are Eq. (1) (model B2), Eq. (3) (for C3), Eq. (5) (for C4 and C6), Eq. (7) (for D3), and Eq. (8) (for D4 and D6). Values for H are generally unique for

each drug/surfactant pair. Values for H for 0.5% SLS, 1% SLS, 2% SLS, 2% PS80, 2% POE10 were 39.7, 83.2, 161, 11.3, and 15.1, respectively. For meloxicam, values for H for 0.5% SLS, 1% SLS, 2% SLS, 2% PS80, 2% POE10 were 1.01, 1.08, 1.29, 3.03, and 2.76, respectively.

Simulation studies were conducted to assess the impact of H value on reduce resistance model P_{app} for each scenario C and D. For scenario C, Eq. (3) was employed to calculate P_{app} over a range of H from 1 to 20. Values of P_d, P_m, and P_r were 193 $\times$ 10^{-6} cm/s, 293 $\times$ 10^{-6} cm/s, and 99.3 $\times$ 10^{-6} cm/s For scenario D, Eq. (7) was similarly employed to calculate P_{app} over a range of H from 1 to 20.

Results and discussion

Overall findings for the most complex scenarios C and D

The objective of the current study was to re-examine previously published HFM flux of griseofulvin and meloxicam to consider the reduced resistance model as an additional contributing mechanism impacting drug flux. For the most complex scenarios C and D for griseofulvin, the preferred model was the reduced resistance model for total drug in both cases, including across all three surfactants SLS, PS80, and POE10. Fig. 2 plots the observed and predicted griseofulvin flux from model D3 in the presence of surfactant on both sides. Model D3 under-predicted flux in the presence of SLS, although predictive accuracy was better for PS80 and POE10. Meanwhile, for the less micelle-incorporated drug meloxicam, the preferred model under scenario D was the simple free drug permeation model (D2), including across surfactants. Fig. 3 plots the observed and predicted meloxicam flux from model D2 in the presence of surfactant on both sides.

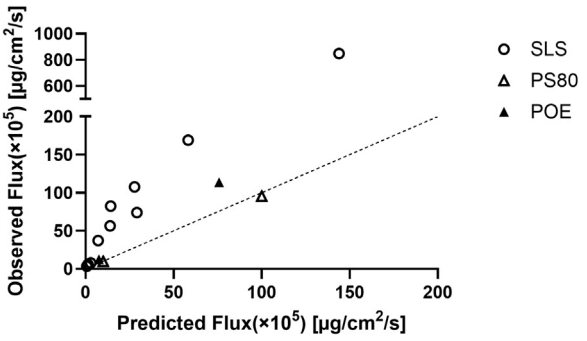


Fig. 2. Observed and predicted griseofulvin flux from model D3 (reduced resistance model for total drug) in the presence of surfactant on both sides. Model D3 was the preferred model when surfactant was present on both sides. Model D3 under-predicted flux in the presence SLS on both sides. Predictive accuracy was better in the presence of PS80 and POE10.

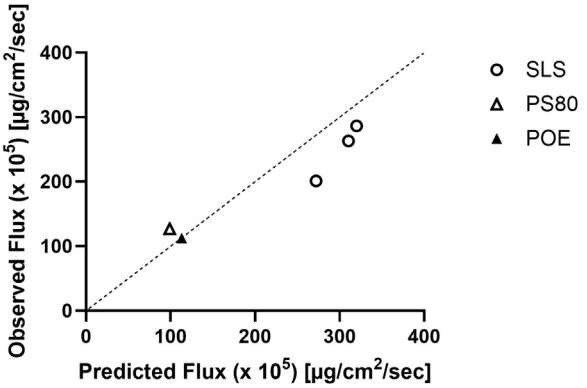


Fig. 3. Observed and predicted meloxicam flux from model D2 (simple free drug permeation model) in the presence of surfactant on both sides. Model D2 was the preferred model when surfactant was present on both sides. Flux was sufficiently well-predicted across different surfactant type using model D2.

Griseofulvin flux: scenario A

In the absence of surfactant, for 6 μg/ml griseofulvin donor concentration, observed griseofulvin flux was 32.1 $\times$ 10^{-5} μg/cm^2/s (Table 2). Assuming simple drug permeation, P_{app} = 53.6 $\times$ 10^{-6} cm/s, which served as the value for P_{app} and P_f in the absence of the reduced resistance model. This value was previously reported.[3]

Griseofulvin flux: scenario B

When 2% SLS was present only in the receiver, for 6 μg/ml griseofulvin donor concentration, the observed flux increased markedly almost 3-fold to 87.3 $\times$ 10^{-5} μg/cm^2/s. Hence, the simple total drug permeation model (B1) underpredicted flux into 2% SLS by about 3-fold (Table 2).

In contrast, inclusion of a reduced resistance component (B2) significantly improved prediction accuracy, with a predicted flux of 114 $\times$ 10^{-5} μg/cm^2/s into 2% SLS.

Griseofulvin flux: scenario C

When 2% SLS was present only in the donor, for 60 μg/ml griseofulvin donor concentration, observed flux was only 4.23 $\times$ 10^{-5} μg/cm^2/s. Hence, the simple total drug permeation model (C1) dramatically overpredicted flux by about 75-fold (Table 2). Models based on free drug concentration (C2) substantially improved predictions.

Incorporation of a reduced resistance model further improved prediction, with C3 (total drug with reduced resistance) performing better than C4 (free drug with reduced resistance). Overall, C3 was the preferred model when surfactant present in donor only. Predicted flux from C3 was 7.11 $\times$ 10^{-5} μg/cm^2/s, in best agreement with observed 4.23 $\times$ 10^{-5} μg/cm^2/s. Predicted flux from C4 was 0.0441 $\times$ 10^{-5} μg/cm^2/s, which was 100-fold too low.

Since C2 and C4 underpredicted griseofulvin flux, C5 and C6 were considered, where SLS P_{DM} values were calculated to be 0.370 $\times$ 10^{-6} cm/s and 0.702 $\times$ 10^{-6} cm/s, respectively.

Griseofulvin flux: scenario D

When 2% SLS was present in both donor and receiver, for 6 μg/ml griseofulvin donor concentration, observed flux was only 3.40 $\times$ 10^{-5} μg/cm^2/s. Hence, the simple total drug permeation model (D1) dramatically overpredicted flux by about 10-fold (Table 2). A similar pattern was observed for PS80 and POE10.

Models based on free drug concentration (D2) substantially lowered predicted flux, including where predicted flux in 2% SLS was 17-fold too low. Similarly, this model was not preferred due to consistent underprediction

Incorporating resistance effects into the model further improved prediction, with D3 (total drug with reduced resistance) performing much better than D4 (free drug with reduced resistance). Overall, D3 was the preferred model when surfactant was present in both compartments. D3 performed better for PS80 and POE10, than for SLS (Fig. 2 and Table 2). For example, for 6 μg/ml griseofulvin donor concentration, predicted flux from D3 for PS80 and POE10 were 10.1 $\times$ 10^{-5} μg/cm^2/s and 7.58 $\times$ 10^{-5} μg/cm^2/s, providing the closest agreement with the observed fluxes of 9.87 $\times$ 10^{-5} μg/cm^2/s and 12.5 $\times$ 10^{-5} μg/cm^2/s, respectively. Their predicted flux from D4 were 0.883 $\times$ 10^{-5} μg/cm^2/s and 0.502 $\times$ 10^{-5} μg/cm^2/s, respectively, which are an order of magnitude too low.

For 6 μg/ml griseofulvin donor concentration in 2% SLS, predicted flux from D3 was 0.719 $\times$ 10^{-5} μg/cm^2/s, closely reflecting the observed value of 3.40 $\times$ 10^{-5} μg/cm^2/s. Predicted flux from D4 was

Table 2
Observed and predicted griseofulvin total flux J_t under different experimental scenarios and competing models.

Griseofulvin solution conc in donor (ug/ml)	Media additive (donor or receiver)	Permeability scenario	Observed J_t ($\times 10^5$) [μg/cm^2/s]	Predicted J_t ($\times 10^5$) [μg/cm^2/s]
6	None	A	32.1 ± 2.3	Not performed
6	2% SLS	B1	87.3 ± 7.09	32.1 ± 2.3
		B2		114 ± 0.03
60	2% SLS	C1	4.23 ± 0.54	321 ± 23
		C2		1.99 ± 0.03
		C3		7.11 ± 0.10
		C4		0.0441 ± 0.0010
6	0.5%SLS	D1	7.80 ± 0.30	32.1 ± 2.3
		D2		0.811 ± 0.015
		D3		2.91 ± 0.01
		D4		0.0737 ± 0.0003
6	1% SLS	D1	5.70 ± 0.10	32.1 ± 2.3
		D2		0.387 ± 0.008
		D3		1.39 ± 0.03
		D4		0.0167 ± 0.0007
6	2% SLS	D1	3.40 ± 0.21	32.1 ± 2.3
		D2		0.199 ± 0.029
		D3		0.719 ± 0.010
		D4		0.00447 ± 0.00001
6	2%PS80	D1	9.87 ± 0.54	32.1 ± 2.3
		D2		2.83 ± 0.04
		D3		10.0 ± 0.1
		D4		0.883 ± 0.003
6	2% POE10	D1	12.5 ± 1.1	32.1 ± 2.3
		D2		2.12 ± 0.04
		D3		7.58 ± 0.13
		D4		0.502 ± 0.018
60	0.5%SLS	D1	74.0 ± 8.1	321 ± 23
		D2		8.11 ± 0.16
		D3		29.2 ± 0.6
		D4		0.736 ± 0.003
60	1% SLS	D1	56.5 ± 2.9	321 ± 23
		D2		3.86 ± 0.08
		D3		13.9 ± 0.3
		D4		0.167 ± 0.007
60	2% SLS	D1	37.1 ± 4.9	321 ± 23
		D2		1.99 ± 0.03
		D3		7.19 ± 0.11
		D4		0.0447 ± 0.0013
60	2%PS80	D1	95.6 ± 1.5	321 ± 23
		D2		28.4 ± 0.4
		D3		100.1 ± 1.5
		D4		8.83 ± 0.26
60	2% POE10	D1	114 ± 11	321 ± 23
		D2		21.3 ± 0.4
		D3		75.8 ± 1.3
		D4		5.02 ± 0.17
120	0.5%SLS	D1	169 ± 13	642 ± 46
		D2		16.2 ± 0.3
		D3		58.3 ± 1.1
		D4		1.47 ± 0.06
120	1% SLS	D1	108 ± 2	642 ± 46
		D2		7.73 ± 0.16
		D3		27.8 ± 0.6
		D4		0.335 ± 0.013
120	2% SLS	D1	82.5 ± 1.9	642 ± 46
		D2		4.14 ± 0.12
		D3		14.3 ± 0.2
		D4		0.0926 ± 0.0021
1200	2% SLS	D1	847 ± 19	6420 ± 460
		D2		41.4 ± 1.2
		D3		143.9 ± 2.1
		D4		0.926 ± 0.021

J_t was not predicted for models A, C5, C6, D5 and D6 since observed J_t was used to estimate P_{app} for those models.

0.00447×10^{-5} μg/cm^2/s, which was about 750-fold too low. Of note, models combining free drug assumption with reduced resistance (i.e., C4 and D4) always severely underpredicted flux, including across the various surfactants in scenario D.

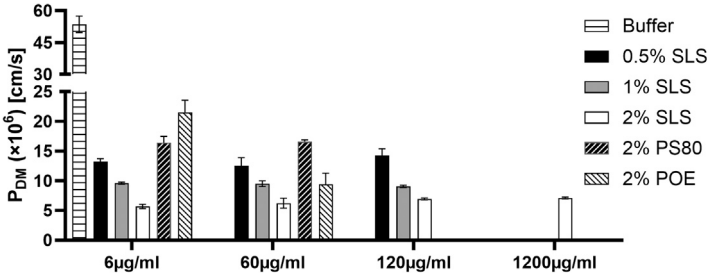


Fig. 4. Drug loaded micelle permeability (P_{DM}) as per scenario D6 (reduced resistance model for free drug and micelle-bound drug permeation) for griseofulvin in presence of surfactant on both sides. Permeability values are very similar to what was previously reported for what is now denoted as model D5. This similarity reflects that the vast majority of drug was not free but micellar bound, and hence not impacted by reduced resistance model for free drug. Free drug permeability is also plotted and denoted as buffer.

Since D2 and D4 underpredicted griseofulvin flux, models D5 and D6 were considered. Fig. 4 shows estimated drug-loaded micelle permeability P_{DM} values from D6. These values are very similar to those of previously reported, for what is now denoted as model D5. That is, the inclusion of reduced resistance effects in D6 had essentially no impact on calculated P_{DM}, since the vast majority of griseofulvin was micelle-bound. Table S1 lists P_{DM} values.

The reduced resistance model as the preferred model for griseofulvin flux across HFM when micelles are present

For griseofulvin, the reduced resistance model for total drug was the preferred model for each scenario B, C, and D. When surfactant was added to receiver, the reduced resistance model predicted flux to increase. When surfactant was added to donor, the reduced resistance model predicted flux to decrease. When surfactant was added to both donor and receiver, the reduced resistance model predicted flux to decrease. The reduced resistance model for total drug always underpredicted flux, except in one case, from about 1.01–6-fold (Table 3).

Models employing free drug as the gradient for flux (e.g., C2 and D2) always underpredicted flux, from about 2–20-fold. A limitation was that this approach requires an estimate of free drug concentration.

In all cases, the reduced resistance model for total drug was more accurate than the free drug model (i.e., model D2) which was the second most preferred model when surfactant was present on both sides (Figure S1).

When surfactant was in both donor and receiver, the reduced resistance model D3 underpredicted flux, particularly for higher values of H (i.e., for SLS than for PS80 or POE10, particularly for higher SLS concentration). This pattern reflects stronger micellar sequestration and higher solubility ratios for 2% SLS ($H \approx 160$) compared with 2% PS80 and 2% POE10 ($H \approx$ 11-15). These findings indicate that, when surfactant is present in both donor and receiver, receiver-side resistance reduction dominated over donor-side micellization, but the balance between these effects depends upon degree of drug incorporation into micelle.

For each scenario C and D, two models considered permeation of drug-containing micelles (i.e., C5 and C6, as well as D5 and D6). In Table 1, these models employ free and not total drug for non-micellar drug permeability. C6 and D6 consider reduced resistance impact on non-micellar drug permeability, while C5 and D5 do not. Using Eq. (6), P_{DM} was calculated, in part by using observed flux, such that a major model analysis outcome was not predicted flux but rather calculated P_{DM}.

SLS P_{DM} values were calculated to be 0.370×10^{-6} cm/s and 0.702×10^{-6} cm/s for C5 and C6, respectively. Surfactant P_{DM} values

Table 3
Observed griseofulvin permeability data across HFM.

Griseofulvin solution conc in donor (ug/ml)	Media additive (donor or receiver)	Preferred model	Solubility ratio H	Observed Permeability (P_{app}) ($\times 10^6$) [cm/s]	Predicted permeability (P_{app}) ($\times 10^6$) [cm/s]	Observed J_t ($\times 10^5$) [μg/cm^2/s]	Predicted J_t ($\times 10^5$) [μg/cm^2/s]
6	Buffer	A	1	53.6 ± 3.9	53.6	32.1 ± 2.3	Not performed
6	2% SLS	B2	161 ± 2	146 ± 0.1	189 ± 0.1	87.3 ± 7.1	114 ± 0.03
60	2% SLS	C3	161 ± 2	0.706 ± 0.008	1.18 ± 0.02	4.23 ± 0.54	7.11 ± 0.10
6	0.5%SLS	D3	39.7 ± 0.8	13.0 ± 0.5	4.86 ± 0.09	7.80 ± 0.30	2.91 ± 0.01
6	1% SLS	D3	83.2 ± 1.7	9.50 ± 0.16	2.32 ± 0.03	5.70 ± 0.10	1.39 ± 0.03
6	2% SLS	D3	161 ± 2	5.67 ± 0.35	1.20 ± 0.01	3.40 ± 0.21	0.719 ± 0.010
6	2%PS80	D3	11.3 ± 0.2	16.4 ± 0.9	16.7 ± 0.03	9.87 ± 0.54	10.0 ± 0.1
6	2% POE10	D3	15.1 ± 0.3	20.9 ± 1.9	12.6 ± 0.02	12.5 ± 1.1	7.58 ± 0.13
60	0.5%SLS	D3	39.7 ± 0.8	12.3 ± 0.1	4.86 ± 0.09	74.0 ± 8.1	29.2 ± 0.56
60	1% SLS	D3	83.2 ± 1.7	9.4 ± 0.5	2.32 ± 0.03	56.5 ± 2.9	13.9 ± 0.3
60	2% SLS	D3	161 ± 2	6.18 ± 0.82	1.20 ± 0.01	37.1 ± 4.9	7.19 ± 0.11
60	2%PS80	D3	11.3 ± 0.2	15.9 ± 0.2	16.7 ± 0.03	95.6 ± 1.5	100.1 ± 1.5
60	2% POE10	D3	15.1 ± 0.3	16.5 ± 1.5	12.6 ± 0.02	114 ± 11	75.8 ± 1.3
120	0.5%SLS	D3	39.7 ± 0.8	14.1 ± 1.0	4.86 ± 0.09	169 ± 13	58.3 ± 1.1
120	1% SLS	D3	83.2 ± 1.7	8.96 ± 0.19	2.32 ± 0.03	108 ± 2	27.8 ± 0.6
120	2% SLS	D3	161 ± 2	6.88 ± 0.16	1.20 ± 0.01	82.5 ± 1.9	14.3 ± 0.2
1200	2% SLS	D3	161 ± 2	7.06 ± 0.15	1.20 ± 0.01	847 ± 19	144 ± 2

Observed apparent permeability and observed flux across the HFM is also listed for each drug-surfactant experiment. From the preferred model D3 (reduced resistance model for total drug), predicted permeability value and predicted flux are listed.

from D5 and D6 are listed in Table S1. Fig. 4 also plots P_{DM} values from D6, which are very similar to values from D5. SLS P_{DM} values were about 5-10 $\times$ 10^{-6} cm/s, or about 10-fold higher than those from C5 and C6. Hence, SLS P_{DM} values were not consistent across experimental scenarios, such that none of these models were preferred. A limitation was that this approach, involving Eq. (6), requires an estimate of free drug concentration.

In the prior analysis of this HFM data involving surfactant in both compartments, the preferred model was D5, which this current analysis rejects in favor of the D3 (i.e., reduced resistance model for total drug).

The simple free drug permeation model as the preferred model for meloxicam flux across HFM when micelles present

Relative to griseofulvin, meloxicam was evaluated as a negative control, since it was much less extensively bound into micelles, per solubility studies. Prior data was not previously analyzed in terms of a preferred model. Meloxicam studies were only conducted in the absence of surfactant, with surfactant in receiver only, and with surfactant in both. Studies with surfactant in donor only were not conducted.

Overall, here, the preferred model for meloxicam permeability across HFM in the presence of surfactant was the simple free drug permeation model D2.

In the absence of surfactant, for 60 μg/ml meloxicam donor concentration, observed meloxicam flux was 285.2 $\times$ 10^{-5} μg/cm^2/s (Table 4). Assuming simple drug permeation, P_{app} = 47.5 $\times$ 10^{-6} cm/s, which served as the value for P_{app} and P_f in the absence of the reduced resistance model. This value was previously reported.[3]

When 2% SLS was present only in the receiver, for 60 μg/ml donor concentration, the observed flux increased markedly about 2-fold to 433.2 $\times$ 10^{-5} μg/cm^2/s. Hence, the simple total drug permeation model (B1) slightly underpredicted flux into 2% SLS by about 1.3-fold (Table 4). Inclusion of a reduced resistance component (B2) improved prediction accuracy, with a predicted flux of 383.1 $\times$ 10^{-5} μg/cm^2/s into 2% SLS.

When 2% SLS was present in both donor and receiver, for 60 μg/ml donor concentration, observed flux was a slightly reduced 201.1 $\times$ 10^{-5} μg/cm^2/s. Hence, the simple total drug permeation model (D1) overpredicted flux by about 1.6-fold (Table 4). A similar pattern was observed for PS80 and POE10, with larger prediction errors due to these surfactants even larger reductions in observed flux.

Model based on free drug concentration (D2) lowered predicted flux, yielding the most accurate prediction of observed flux when surfactant was present (Table 5). Drug was not highly bound by SLS and modestly bound by 2% PS80 and 2% POE10. Fig. 3 plots observed and predicted meloxicam flux from model D2 (simple free drug permeation model) in the presence of surfactant on both sides. There was good agreement, with some tendency to overpredict flux for SLS. Model D2 was the preferred model when surfactant was present on both sides.

Table 4
Observed and predicted meloxicam total flux J_t under different experimental scenarios and competing models.

Meloxicam solution conc in donor (ug/ml)	Media additive (donor or receiver)	Permeability scenario	Observed J_t ($\times 10^5$) [μg/cm^2/s]	Predicted J_t ($\times 10^5$) [μg/cm^2/s]
60	None	A	285.2 ± 32.2	Not performed
60	2% SLS	B1	433.2 ± 12.8	321.4 ± 23.0
		B2		383.1 ± 7.9
60	0.5% SLS	D1	286.6 ± 16.9	321.4 ± 23.0
		D2		319.8 ± 10.4
		D3		322.2 ± 4.7
		D4		320.2 ± 5.7
60	1% SLS	D1	263.3 ± 25.1	321.4 ± 23.0
		D2		303.2 ± 6.4
		D3		329.6 ± 2.8
		D4		310.6 ± 4.0
60	2% SLS	D1	201.1 ± 23.6	321.4 ± 23.0
		D2		250.2 ± 7.5
		D3		349.6 ± 2.3
		D4		272.0 ± 6.5
60	2% PS80	D1	127.1 ± 5.61	321.4 ± 23.0
		D2		106.4 ± 6.6
		D3		297.9 ± 5.6
		D4		98.8 ± 5.2
60	2% POE10	D1	112.4 ± 8.23	321.4 ± 23.0
		D2		116.4 ± 4.4
		D3		312.2 ± 5.9
		D4		113.2 ± 6.4

J_t was not predicted for models A, C5, C6, D5 and D6 since observed J_t was used to estimate P_{app} for those models.

Table 5
Observed meloxicam permeability data across HFM.

Meloxicam solution conc in donor (ug/ml)	Media additive (donor or receiver)	Preferred model	Observed Permeability (P_{app}) ($\times 10^6$) [cm/s]	Predicted permeability (P_{app}) ($\times 10^6$) [cm/s]	Observed J_t ($\times 10^5$) [$\mu g/cm^2/s$]	Predicted J_t ($\times 10^5$) [$\mu g/cm^2/s$]
60	Buffer	A	47.5 ± 5.4	53.6	285 ± 32	Not performed
60	SLS 2%	B2	72.2 ± 2.1	47.9 ± 1.5	433 ± 12	383 ± 8
60	SLS 0.5%	D2	47.8 ± 2.8	46.4 ± 3.4	287 ± 17	320 ± 10
60	SLS 1%	D2	43.9 ± 4.2	43.2 ± 5.3	263 ± 25	303 ± 6
60	SLS 2%	D2	37.2 ± 3.9	64.0 ± 3.2	201 ± 24	250 ± 8
60	PS80 2%	D2	21.2 ± 0.9	51.7 ± 3.1	127 ± 6	106 ± 7
60	POE10 2%	D2	18.7 ± 1.4	47.9 ± 1.5	112 ± 8	116 ± 4

Preferred model result is listed. Preferred model was B2 and D2. From the preferred model D2 (simple free drug permeability model), predicted permeability value and predicted flux are listed.

The reduced resistance model for total drug concentration (D3) was not preferred since it overpredicted flux by about 1.1−3-fold (Tables 4 and S2). Larger errors occurred for PS80 and POE10.

The reduced resistance model for free drug concentration (D4) yielded similar predictions to those of D2 (Table 4 and Figure S2), although was not preferred since D2 is simpler than D4.

Model D5 and D6 were not considered since the simple free drug permeation model D2 was sufficient and exhibited some tendency to overpredict flux for SLS, which drug-bound micelle permeation could not address.

Effect of solubility ratio (H) on apparent permeability

Using Eq. (3) and 7, Fig. 5 shows the simulated P_{app} as a function of the solubility ratio H when surfactant is present only in the donor (scenario C) and when present in both donor and receiver (scenario D). Under each scenario, P_{app} decreases with increasing H, although P_{app} increases slightly when $H = 2$ for scenario D. Simulation extending beyond $H = 20$, such as $H = 200$, reflect a progressively asymptotic profile.

P_{app} for scenario C decreases immediately (i.e., at low H, including $H = 2$) since Eq. (3) only allows P_{app} to decrease via the H/P_d term. Meanwhile, P_{app} for scenario D increases immediately (i.e., at low H, including $H = 2$) since Eq. (7) allows for an increase in P_{app} via the $1/(HP_m) + 1/(HP_r)$ terms.

Comparative interpretation and implications for HFM permeability modeling

These results demonstrate that drug permeation across HFM in surfactant-containing systems is governed by a compound-specific interplay between donor-side micellization and receiver-side resistance reduction. In the absence of surfactant, the simple flux model was applied to griseofulvin flux across HFM (scenario A), yielding P_{app} values similar to other drugs. The preferred model for scenario B, C, and was the reduced resistance model for total drug. For scenario D, donor micellization strongly suppressed free drug concentration, but receiver-side surfactant markedly enhanced membrane and receiver permeability components, via reduced resistance. The reduced resistance model for total drug best reconciled these opposing effects.

In contrast, meloxicam exhibited weak micellar binding, such that free drug permeation alone sufficiently described flux transport behavior across all surfactant tested conditions (i.e., scenario B and D).

Collectively, this modeling supports the view that drug concentration alone is not a reliable predictor of flux. Instead, it is chemical potential which is the driving force for diffusion in HFM. The agreement between predicted and observed fluxes for griseofulvin indicates that the use of the solubility ratio H is an appropriate level of theory to capture this effect. More complex models which may consider the free drug fraction, boundary layer thickness, or effective diffusivity are not required under the current experimental conditions. These results also corroborate that increases in solubility due to reduced chemical activity do not necessarily result in a permeability advantage.[5,6] Even though the resistance-based models were not preferred in the case of meloxicam, this does not undermine the importance of considering the effect of an additive on chemical potential. The impact of SLS on meloxicam solubility is only very modest and thus, unlike griseofulvin, the competing models tended towards very similar values (Table 5). This reflects the fact that the meloxicam chemical potential gradient is not greatly altered by SLS and thus simpler models which do not consider solubilization are sufficient to approximate flux in this scenario.

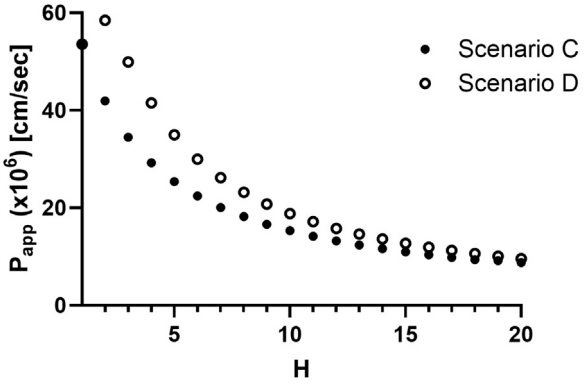


Fig. 5. Simulated P_{app} as a function of H for the reduced resistance model under scenarios C and D. Scenario C is when surfactant is present only in the donor. Scenario D is when surfactant is present in both donor and receiver. P_{app} decreases faster for C than D, which slightly increased when $H = 2$.

Conclusion

Surfactants exert opposing effect on drug permeation across membranes, including HFM, thereby complicating the interpretation of flux data generated under different conditions. Through a pooled analysis of published griseofulvin and meloxicam HFM datasets, this study points towards systematic effects by considering both donor-side micellar sequestration and receiver-side resistance reduction within a reduced resistance model.

For griseofulvin, higher micelle incorporation in the donor compartment substantially reduced flux, while surfactant-mediated solubilization in the receiver markedly increased flux. Reduced resistance models incorporating differential solubility effect between compartments, via the ratio of drug solubility in surfactant versus buffer, best predicted flux across all experimental scenarios, including conditions where surfactant was present in both donor and receiver. Notably, the experimental data were explained without invoking explicit micellar permeation across the membrane. In contrast, meloxicam, which exhibited less micelle incorporation, showed moderate

changes across surfactant conditions. Taken together, these findings underscore the importance of accounting for solubility-driven resistance effects when interpreting permeability data in the presence of surfactants. Reliance on calculated free drug concentration alone led to less accurate predictions, particularly for highly micelle-bound compounds. The reduced resistance framework improved flux prediction.

Declaration of competing interest

There are no conflicts of interest for these authors to declare.

CRediT authorship contribution statement

Roshni P. Patel: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jack D. Murray:** Investigation, Methodology, Writing – review & editing. **Brendan T. Griffin:** Writing – review & editing. **James E. Polli:** Funding acquisition, Methodology, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xphs.2026.104318.

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