Pharm Res (2010) 27:2646–2656
DOI 10.1007/s11095-010-0264-x

RESEARCH PAPER

Predicting the Effect of Fed-State Intestinal Contents on Drug Dissolution

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Received: 29 April 2010 / Accepted: 30 August 2010 / Published online: 21 October 2010

ABSTRACT

Purpose There are several endogenous and exogenous species in the gastrointestinal (GI) tract which can act as solubilizing agents and thereby affect drug dissolution. The purpose of this study is to understand food effects on drug dissolution and provide insight into their anticipated overall effect on absorption and bioavailability.

Methods Dissolution kinetics of 15 drugs of variable logP, charge, and molecular weight were tested in simulated intestinal environment. The ability of a film-equilibrium-based model to predict the influence of a simulated intestinal environment on drug dissolution was examined.

Results The most significant improvement in dissolution kinetics and solubility (up to 6-fold) was evident with highly hydrophobic compounds (logP > 4). Improvement in solubility did not always constitute improvement in dissolution kinetics on a relevant time scale. Comparison of simulation and experimental results indicates that a model considering micelle partitioning as a pseudo-equilibrium process can predict trends in the influence of food-related solubilizing agents on drug dissolution kinetics.

Conclusions The significance of food-related solubilizing agents to drug dissolution is not always obvious, as it depends on multiple physicochemical parameters; however, simple modeling may provide insight into food effects on dissolution and, ultimately, overall absorption and bioavailability of compounds considered for oral formulation.

KEY WORDS biorelevant media · dissolution · food effect · mathematical modeling

INTRODUCTION

More than 40% of compounds identified as potential drugs are classified as poorly soluble (1). Because dissolution is one of the important processes affecting drug absorption in the gastrointestinal (GI) tract, poorly soluble compounds

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can have low oral absorption as well as low bioavailability. Drug delivery technologies such as cyclodextrins and lipid-based systems are frequently used to aid in drug dissolution in the GI tract. Delivery of a poorly soluble compound with sufficient bioavailability often depends on the selection and proper formulation of the drug delivery technology. In addition, endogenous and exogenous species present in the GI tract can aid in drug dissolution to a certain extent depending on the physical and chemical properties of the compound (2). After food intake, bile salts secreted into the GI tract form endogenous micelles. Fats in food are also digested and form vesicles and emulsions (3). The physical and chemical properties of intestinal contents in the fed state can significantly alter the bioavailability of many compounds (4). While there are multiple potential mechanisms for overall food influence on bioavailability, one way in which digestion products interact with drug is by enhancing dissolution kinetics and solubility.

Physiologically based models predicting drug absorption in the GI tract have obtained much attention in recent years (5–11). For example, programs such as Gastroplus® (Simulations Plus, Lancaster, CA) and Intellipharm® (Intellipharm, Niantic, CT) are simulation software programs which predict oral drug absorption. Such programs quantitatively and dynamically consider processes occurring in the GI tract (e.g. dissolution, precipitation and permeation into the enterocytes of the intestinal wall). The input to such models includes the physicochemical properties of the drug, such as pKa, solubility, diffusion coefficient and effective permeability, and physiological variables such as pH values, transit times, volumes, lengths, and, when applicable, expression levels and Michaelis-Menten constants for enzymes and transporter proteins affecting drug absorption (12,13). Predicting *in vivo* drug absorption by means of models requires prediction of *in vivo* drug solubility and dissolution, which should reflect the influence of endogenous and exogenous species in the GI tract. However, a dissolution expression in the form of the Noyes-Whitney expression is often utilized, which may incorporate the equilibrium solubility of the drug in the presence of drug delivery carriers or endogenous lipids, but not necessarily explicitly consider the physical interactions between drug and these species. The influence of cyclodextrins (CD) on drug dissolution as well as absorption in the GI tract was recently examined both theoretically and experimentally (14). It was concluded that a modified dissolution expression considering complexation with CD as a pseudo-equilibrium process and accounting for both flux of free and complexed drug away from a dissolving surface could reasonably describe dissolution kinetics in the presence of CD in solution. Partitioning into micelles generally involves association of multiple drug molecules with a single micelle (as opposed to typically 1:1 complexation between drug and CD). However, if this process is relatively rapid compared to dissolution, it may be considered as a pseudo-equilibrium in theoretically considering its influence on dissolution kinetics.

In order to mimic drug dissolution in the GI tract environment *in vitro*, biorelevant fluids are used (2). Several media have been proposed to simulate the fasted and fed state intestinal fluids (2). Recently, Jantratid *et al.* updated the compositions of biorevelant media to better imitate the physical and chemical features of gastrointestinal fluid under fed and fasted conditions. Different media were proposed to represent "early," "medium" and "late" phases of digestion in stomach and small intestine (15).

In this study, for the purpose of comparing drug dissolution kinetics in fasted and fed states, Fasted-State Simulated Intestinal Fluid (FaSSIF-2) and Fed-State Simulated Intestinal Fluid (FeSSIF-2), which represent the conditions in the proximal small intestine, were selected from Jantratid *et al.* Simulated Intestinal Fluid (SIF) was also used to compare drug dissolution kinetics in FaSSIF-2 and FeSSIF-2, media containing bile salts and digestion products, to dissolution in a simple buffer lacking lipids. A film-equilibrium model (16,17), similar to the Higuchi model, describing the influence of interacting colloids on transport rates (13), was developed and utilized to predict drug dissolution kinetics in the presence of bile salt-lecithin micelles. In the model, drug partitioning with micelles was considered as a pseudo-equilibrium process. Fifteen compounds were selected based on physical and chemical property values (i.e. logP, pKa and molecular weight) specified by an experimental design. The dissolution kinetics of each compound were measured in both FaSSIF-2 and FeSSIF-2, and the ability of the simple film-equilibrium model and pseudo-equilibrium assumption to predict the influence of simulated intestinal contents on dissolution kinetics was assessed. The relation of the partition coefficient in intestinal micellar species to drug properties (logP, charge, MW) was investigated.

MODEL DEVELOPMENT AND SIMULATIONS

The film-equilibrium model considers micelle-drug partitioning in the unstirred boundary layer at the surface of the dissolving solid drug particle as a pseudo-equilibrium process described by a constant, K (Eq. 1):

$$K = \frac{[C_{drugM}]}{[C_D][C_M]} \tag{1}$$

where $[C_D]$, $[C_M]$, and $[C_{drugM}]$ are concentrations of drug, total micelle and drug-micelle complex, respectively. Both free drug and drug-loaded micelles diffuse across the boundary layer to the bulk solution (16,17) (Fig. 1).

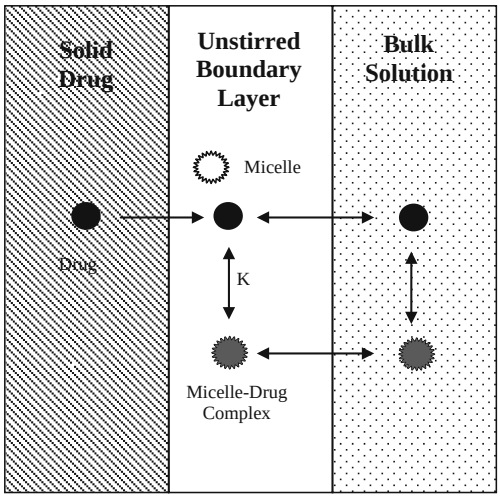

Fig. 1 Schematic of film-equilibrium model.

Relation of Free and Total Drug Concentration in Solution to Micelle Concentration

At each point in time, the concentrations of each species (free and micelle-partitioned drug) in the intestinal lumen, assumed to be well-mixed, can be related by a mass balance on drug:

$$\left[C_{solution,total}\right] = [C_D] + \left[C_{drugM}\right] \tag{2}$$

Equations 1 and 2 can be combined to eliminate [C_{drugM}] and relate [C_D], free drug concentration in solution, to total drug in solution and total micelle concentration:

$$[C_D] = \frac{[C_{solution,total}]}{1 + K[C_M]} \tag{3}$$

Drug Dissolution in the Presence of Micelles

Dissolution kinetics of the drug in the presence of micelles is described by an expression similar to the Noyes-Whitney equation, assuming a linear concentration gradient in the unstirred boundary layer. It is assumed that free drug and micelle-drug complex are in equilibrium in the boundary layer. Thus, the flux of the drug to the medium is expressed by the sum of the flux of free drug and the flux of drug-micelle complex, where D_{drug} and D_{solty} are drug diffusivity and drug solubility, respectively (Eq. 4):

$$\frac{dC_{drug,diss}}{dt} = -\frac{k_{drug}}{V_{lumen}}\left(D_{drug}([D_{solty}] - [C_D]) + D_{drugM}([drugM_{surf,drug}] - [C_{drugM}])\right) \tag{4}$$

This is similar to an expression developed by Higuchi to describe the effects of interacting colloids on transfer rates; the main difference in our approach is that we are explicitly calculating the partitioned drug concentration ([$drugM_{surf,drug}$]) over time using the equilibrium partitioning expression (Eq. 1) and the free drug concentration ([D_f]) determined by mass balance, rather than expressing partitioned drug concentration as a function of variable ratio of partitioned solute (drug) per mole of colloid (micelle) (13). This expression is distinct from expressions previously developed to describe dissolution kinetics in the presence of micelles (17,18) which considered a single flux of drug, including both free drug and drug-loaded micelles. The diffusion coefficient in these cases was represented as a weighted diffusion coefficient between that of free drug and micelles, and the driving force was the difference between equilibrium drug solubility in the micelle solution and total drug in solution. In contrast, here the separate fluxes of free and micelle-associated drug are explicitly considered, each with a distinct diffusion coefficient, which reflects the physical nature of the system.

Since the dissolution expression is essentially a linearized form of Fick's law, the drug dissolution constant, k_{drug}, can be expressed as

$$k_{drug} = \frac{A^T_{drug}}{h_{drug}} \tag{5}$$

where A^T_{drug} is total drug surface area, and h_{drug} is the thickness of the unstirred boundary layer surrounding the drug particles. For the purpose of estimating A^T_{drug} for a given mass of solid drug, uniform spherical particles with a known radius at time of dosing are assumed. The surface area therefore depends on the radii of the dissolving particles, which can be calculated from the particle number (known from initial dose and particle radius at the time of dosing) and mass of solid drug remaining at a given period of time after dosing. The volume of a drug particle is

$$V_{particle} = \frac{4}{3}\pi r^3_{drug} \tag{6}$$

By using the mass ($m_{drug,solid}$), density (ρ), and number of particles (N_{drug}) in the intestinal lumen, the volume of each particle can be expressed as

$$V_{particle} = \frac{m_{drug,solid}}{N_{drug}\rho_{drug}} \tag{7}$$

Combining Eqs. 6 and 7 and solving for r_{drug} yields

$$r_{drug} = \left(\frac{3m_{drug,solid}}{4\pi N_{drug}\rho_{drug}}\right)^{1/3} \tag{8}$$

Total surface area is, therefore,

$$A^T_{drug} = N_{drug}4\pi\left(\frac{3m_{drug,solid}}{4\pi N_{drug}\rho_{drug}}\right)^{2/3} \tag{9}$$

From Eq. 1 and the assumption that partitioning is at equilibrium everywhere, the concentration of drug-micelle complex at the surface of the dissolving drug particle can be found:

$$K = \frac{[drugM_{surf,drug}]}{D_{solty}[M]} \quad (10)$$

NUMERICAL SOLUTIONS TO THE MODEL EQUATIONS

The mathematical expressions used in the model were incorporated into MATLAB® code, and a fixed-step Runge-Kutta method with one-second time steps was used to integrate the differential equation describing drug dissolution over time. At each point in time after dosing, the concentrations of free as well as micelle-partitioned drug are calculated using mass balance on drug as well as the partitioning equilibrium expression, as described above. For that same time interval, the dissolution rate is calculated and used to determine, by mass balance, the total amounts of drug (partitioned and free) in the dissolution apparatus at the beginning of the next time interval. All parameters used for the simulations are shown in Tables I and II. Particle size (radius) of all compounds was taken as 35 μm in the simulations.

MATERIALS AND METHODS

Triamcinolone, thymine, 4-aminobenzoic acid, dipyridamole, atropine, indoprofen, 2-naphthol, haloperidol, spironolactone, phenylbutazone, lecithin, glycerol monooleate and sodium oleate were purchased from Sigma (St. Louis, MO). Molecular weights of all drug compounds are presented in Table III. Fluorene was purchased from Aldrich (St. Louis, MO). Iopanoic acid was purchased from MP Biomedicals, LLC (Solon, OH). Griseofulvin was purchased from Fluka (St. Louis, MO). Sodium taurocholate was purchased from Pfaltz & Bauer, Inc. (Waterbury, CT). All salts except potassium dihydrogen phosphate used in simulated intestinal fluids were purchased from Fisher Scientific (Pittsburgh, PA). Potassium dihydrogen phosphate was purchased from Alfa-Aesar (Ward Hill, MA). All salts used for the simulated fluids were reagent grade, and deionized water was used to prepare all solutions.

Table I Contents of Fasted and Fed Simulated Intestinal Fluids

	FaSSIF	FeSSIF
Sodium Taurocholate	3 mM	10 mM
Lecithin	0.2 mM	2 mM
Maleic Acid	19.12 mM	55.02 mM
NaOH	34.8 mM	81.7 mM
NaCl	68.6 mM	125.5 mM
Sodium Oleate	N/A	0.8 mM
Glycerol Monooleate	N/A	5 mM

Table II Value Ranges of Compound Properties Used in the Statistical Model

	Low (−1)	Intermediate (0)	High (1)
LogP	< 0	>1, <3	<4
MW	>100, <150	>250, <350	>400
Charge @ pH = 6.5	Negative	Neutral	Positive

PREPARATION OF SIMULATED INTESTINAL FLUIDS

FaSSIF-2 and FeSSIF-2 were prepared as described by Jantratid *et al.* (15). Hereafter, FaSSIF-2 and FeSSIF-2 will be referred to as "FaSSIF" and "FeSSIF," respectively. Contents of FaSSIF and FeSSIF are shown in Table II. As a control, simulated intestinal fluid (SIF), which does not contain sodium taurocholate, lecithin or any lipids, was prepared according to US Pharmacopeia IVX. 250 mL of 0.2 M potassium dihydrogen phosphate solution was prepared, and 118 mL of 0.2 M sodium hydroxide was added to the solution. Water was added to bring the solution to 1000 mL. pH values of all simulated fluids were adjusted to 6.5. Particle size and size distributions of FaSSIF and FeSSIF were measured by light scattering (90PlusBI-MAS/Zeta Pal).

DISSOLUTION EXPERIMENTS

In dissolution experiments, excess amount of solid drug was added to a stirred beaker containing 20 mL of FaSSIF, FeSSIF or SIF at 37°C. Most doses ranged from 10 to 100 mg of drug, but some were greater or less depending on amount needed to achieve a saturated solution, accuracy of weighing small amounts of drug, and resource constraints. The dose was taken into account in each simulation (and was used to calculate initial surface area for dissolution). The doses (mg) used in SIF, FaSSIF, and FeSSIF, respectively, for each compound were Triamcinolone (50, 50, 50), Thymine (150, 150, 150), 4-aminobenzoic acid (4100, 5000, 10000), Dipyridamole (25, 25, 90), Atropine (60, 150, 150), Indoprofen (30, 30, 35), Phenytoin (20, 20, 60), 2-Naphthol (60, 60, 60), Haloperidol (7, 7, 20), Spironolactone (15, 20, 35),

Table III Compounds Chosen for Dissolution Testing and Properties Used in the Simulations

Compound	LogP[a]	Charge at[a] pH 6.5	Molecular[a] Weight (g/mole)	Diffusion[b] Coefficient (cm^2/s)x10^6	K(M^{-1})[c]	Solubility[d] in SIF (mg/mL)	Solubility[d] in FaSSIF (mg/mL)	Solubility[d] in FeSSIF (mg/mL)
Triamcinolone	−0.20	Neutral	398.5	2.7	10.9	0.13 ± 0.012[e,f]	0.12 ± 0.002[f]	0.15 ± 0.008
Thymine	−0.10	Neutral	126.1	7.4	16.3	5.2 ± 0.14	6.1 ± 0.83	6.2 ± 0.2
4-aminobenzoic acid	0.79	Negative	137.1	7.7	51.8	18.5 ± 2.2[e,f]	27.1 ± 1.7[f]	37.5 ± 0.1
Dipyridamole	1.35	Positive	504.6	2.1	333	0.0090 ± 0.002[f]	0.012 ± 0.001[f]	0.060 ± 0.001
Atropine	1.69	Positive	289.4	3.2	63.1	2.7 ± 0.37	6.0 ± 1.0	6.7 ± 2.6
Indoprofen	2.06	Negative	281.3	3.6	31.5	0.57 ± 0.13	0.80 ± 0.003	0.97 ± 0.15
Phenytoin	2.16	Neutral	252.3	3.8	844	0.0036 ± 0.0002[f]	0.020 ± 0.002[f]	0.060 ± 0.007
2-Naphthol	2.99	Neutral	114.1	6.3	89.1	0.95 ± 0.1[e,f]	1.84 ± 0.1	2.3 ± 0.3
Haloperidol	3.01	Positive	375.9	2.5	325	0.070 ± 0.009[f]	0.10 ± 0.05[f]	0.46 ± 0.07
Spironolactone	3.12	Neutral	416.7	2.3	100	0.026 ± 0.0004[f]	0.033 ± 0.004[b]	0.072 ± 0.003
Griseofulvin	3.50	Neutral	352.8	3.0	191	0.0086 ± 0.0001[e,f]	0.020 ± 0.003[f]	0.040 ± 0.002
Phenylbutazone	3.95	Negative	308.4	2.9	24.3	0.58 ± 0.2	0.65 ± 0.07	0.84 ± 0.09
Fluorene	4.16	Neutral	166.2	5.2	3280	0.0010 ± 0.0001[f]	0.0018 ± 0.0002[f]	0.060 ± 0.001
Iopanoic Acid	4.19	Negative	570.9	3.3	616	0.050 ± 0.002[f]	0.093 ± 0.004[f]	0.58 ± 0.03
Clofazimine	6.68	Positive	473.4	2.1	2310	0.00060 ± 0[e,f]	0.0025 ± 0.0005[e,f]	0.025 ± 0.002

[a] SciFinder® calculated value

[b] Calculated using Wilke-Chang (Eq. 12)

[c] Calculated using Eq. 11

[d] Experimentally measured as explained in "Materials and Methods"

[e] Solubility in SIF is statistically different from solubility in FaSSIF ($p < 0.05$).

[f] Solubility is significantly different from solubility in FeSSIF ($p < 0.05$).

Griseofulvin (25, 25, 70), Phenylbutazone (13, 20, 20), Fluorene (10, 10, 25), Iopanoic Acid (60, 60, 100), Clofazimine (10, 10, 100). The experiments were conducted on a stirring hot plate at 150 rpm. Samples (0.5 mL) were withdrawn from the beaker at certain time intervals and the volume of medium withdrawn was replaced by the equivalent volume of medium. Samples were filtered immediately through a 0.45 μm nylon filter and analyzed via HPLC to determine the concentration of drug in solution. The experiments as well as HPLC measurements were conducted in duplicate. The sampling and dilution were taken into account in the developed model and found to have minimal effect on the resulting dissolution profiles.

Drug solubilities in all media were taken as the concentrations at which drug leveled off in the dissolution tests. Concentrations of clofazimine, griseofulvin and fluorene in SIF during the dissolution tests were too low to be detected by HPLC. Dissolution test results of these compounds in SIF were therefore not reported. To measure solubilities of these compounds in SIF for the purpose of calculating *K*, an excess amount of drug was added to 1 mL of SIF and mixed overnight at 37°C on a rotating shaker. After filtration, the concentration of drug was determined via HPLC.

HPLC ANALYSIS

The concentrations of all compounds in simulated fluids were determined using HPLC with a photodiode detector (Shimadzu, Japan). The analytical column used was Agilent Zorbax RX-C18 4.6×75 mm, 3.5 μ. The column temperature was maintained at 30°C, and the flow rate was 1 mL/min. The mobile phase contained distilled water with 0.15% TFA: acetonitrile (90:10 to 10:90 over 12 min) for all compounds except thymine and iopanoic acid. For thymine, the mobile phase was 0.001 M phosphate buffer at pH 5.7: methanol (90:10 to 10:90 over 12 minutes), and for iopanoic acid it was 0.15% TFA: methanol (90:10 to 10:90 over 12 min).

CALCULATION OF EFFECTIVE DRUG-MICELLE PARTITIONING COEFFICIENT (*K*)

Effective drug-micelle partitioning coefficient, *K*, was calculated using the measured drug solubilities and total surfactant concentrations in all media (19). From Eqs. 1 and 2,

$$\frac{[D_{solution,total}]}{D_{solty}} = K[M] + 1 \tag{11}$$

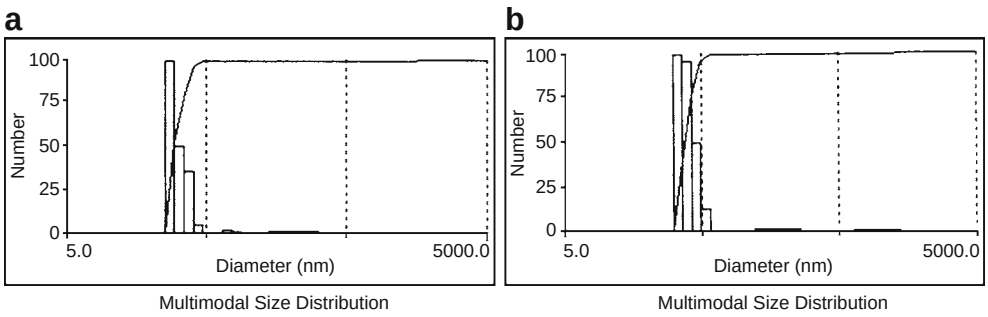

Fig. 2 Particle size and size distribution measurements of FaSSIF (**a**) and FeSSIF (**b**).

where D_{solty} and $[D_{solution,total}]$ are the solubility of the compound in SIF without any lipids and total drug concentration (free and micelle partitioned) in solution in each media, respectively. K is the slope of the graph of $[D_{solution,total}]/D_{solty}$ *vs.* $[M]$.

ESTIMATION OF DRUG AND MICELLE DIFFUSIVITIES

Diffusivities of all compounds used in simulations were estimated by the Wilke-Chang equation (20):

$$D_{AB} = 7.4x10^{-8}\frac{\sqrt{\Psi_B MW_B}}{\eta_B \overline{V}_A^{0.6}}T \tag{12}$$

where D_{AB} is the diffusivity of compound A in solvent B (cm^2/s), Ψ_B is the constant which accounts for solvent/solvent interactions (2.6 for water), T is temperature (K), η_B is the viscosity of solvent B (cP), MW_B is molecular weight of solvent B (g/mol), and V_A is the molar volume of compound A.

In the calculations, the solvent was assumed to be water, and viscosity of water at 37°C (0.697 cP) was used.

Micelle diffusivity was estimated using the Stokes-Einstein equation and the measured mean particle size (17).

$$D_{AB} = \frac{kT}{6\pi\eta_B.r_A} \tag{13}$$

where D_{AB} is the diffusivity of compound A in solvent B (cm^2/s), K is the Boltzman constant (1.3806×10^{-23} m^2 kg s^{-2} K^{-1}), T is temperature (K), η_B is the viscosity of solvent B (cP), and r_A is the hydrodynamic radius of the particle.

STATISTICAL MODEL FOR COMPOUND SELECTION AND ANALYSIS OF VARIANCE (ANOVA)

Fifteen compounds were selected for the dissolution tests from a set of drug-like compounds according to properties hypothesized to influence partitioning into micelles: molecular weight, charge and logP. pKa of the compound (obtained from SciFinder™) was used to obtain the charge at pH 6.5, which was the pH of simulated fluids used in the dissolution tests. Compounds were selected based on statistical design of experiment; value ranges used in the model are shown in Table II, and compounds and their specific properties are listed in Table III. To understand the effect of each parameter (logP, molecular weight and charge) on the micelle partitioning coefficient, an ANOVA test was run using JMP®. ANOVA with Tukey's post-hoc test was used to test statistical significance between solubilities measured in different media.

RESULTS AND DISCUSSION

Particle Size Measurements of FaSSIF and FeSSIF

Particle size and size distribution of FaSSIF and FeSSIF were measured, and mean particle size for both simulated fluids was found to be 31 nm (Fig. 2). This measured diameter indicates that micelles were formed in FaSSIF and FeSSIF used in the dissolution tests (21).

ANOVA Test

In order to investigate the effect of each parameter (logP, MW and charge) on the measured partition coefficient, an ANOVA test was run in JMP® (Table IV). Only logP had a significant effect on drug-micelle partition coefficient, K (P= 0.0153). LogP has previously been shown to have a significant effect on improvement in solubility in both model

Table IV ANOVA Test Results

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	202	551	0.37	0.72
MW	−1.88	1.63	−1.15	0.27
LogP	360	125	2.87	0.015[a]
Charge	287	290	0.99	0.34

[a] Statistically significant

biorelevant and actual intestinal fluids (22). It was somewhat surprising that net compound charge (positive, negative, neutral) did not significantly impact the K value.

Dissolution Data Analysis

Dissolution kinetics were measured for the 15 compounds shown in Table III. Simulations were run to test the ability of a simple model based on the film equilibrium model to describe the influence of micelles present in simulated intestinal fluids on the dissolution kinetics of various drugs. Comparisons of simulation predictions with experimental dissolution profiles are shown below according to logP values, as logP had a significant influence on the ability of drugs to partition into micelles in simulated fluids.

Low logP(< 0)

For triamcinolone and thymine, which are compounds with low logP, improvement in solubility as well as dissolution kinetics is minimal (Fig. 3). As these compounds are hydrophilic, their dissolution kinetics are already relatively fast, and micelle partitioning is very low. The micelle partitioning coefficients calculated for triamcinolone and thymine are 10.9 and 16.3 M^{-1}, respectively. While qualitatively describing dissolution kinetics accurately, model predictions for dissolution kinetics of thymine in FaSSIF and FeSSIF are somewhat faster than those obtained in the experiments. This could be due to multiple simplifying assumptions in the model; for example, the assumed drug particle size (35 μm) may be smaller than the actual particle size, as a single uniform particle size was assumed for all compounds tested. In addition, micelle size (31 nm) was assumed to be constant and not dependent on the drug, which may also introduce error. Employment of measured particle size for drug and drug-micelle system, and consideration of particle size distribution for each compound would likely provide more accurate predictions using the developed model. Agglomeration of drug during experiments containing excess solid drug could, however, decrease the advantage of carefully measuring particle size in enabling accurate predictions.

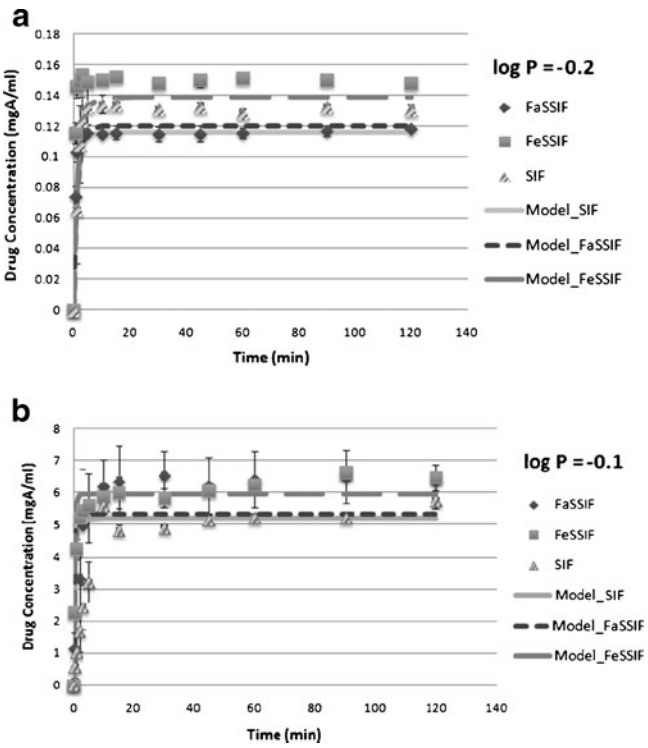

Fig. 3 Comparison of dissolution kinetics of low logP compounds, triamcinolone (**a**) and thymine (**b**), in SIF, FaSSIF and FeSSIF with model predictions.

Medium logP(> 1, < 3)

For medium logP value compounds, significant improvement in solubility was observed for all compounds from SIF to FeSSIF due to micelle partitioning. However, improvement in dissolution kinetics (as indicated by initial slope of dissolution curve) from SIF to FeSSIF was only evident for dipyridamole, phenytoin and haloperidol, which have higher K values compared to other compounds shown in Fig. 4. K values calculated for dipyridamole, phenytoin and haloperidol are 332.2, 843.5 and 325 M^{-1}, respectively (Table III). Since K indicates the degree of drug-micelle partitioning, compounds with high K values are anticipated to dissolve faster in fed state than in fasted state. Dissolution rates and solubilities of dipyridamole and haloperidol were not observed to increase in FaSSIF compared to SIF; however, there was a significant improvement in both solubility and dissolution rate in FeSSIF due to greater amount of micelles present in FeSSIF compared to FaSSIF. Results indicate that dipyridamole, haloperidol and phenytoin have more potential for food effects on their dissolution kinetics in the GI tract compared to other medium-logP compounds. A compound's potential for food effects in the GI tract should be considered at the formulation stage, since variations in drug dissolution can significantly affect oral absorption and bioavailability.

High logP(> 4)

All high logP value compounds showed improvements in dissolution rate in FeSSIF compared to FaSSIF and SIF due to micelle partitioning (Fig. 5). As with certain medium logP compounds (i.e. indoprofen and 2-naphthol, Fig. 4b and f, respectively), there was some discrepancy between the experimental and theoretical values at which the dissolution curves for fluorine (Fig. 5b) in FaSSIF leveled

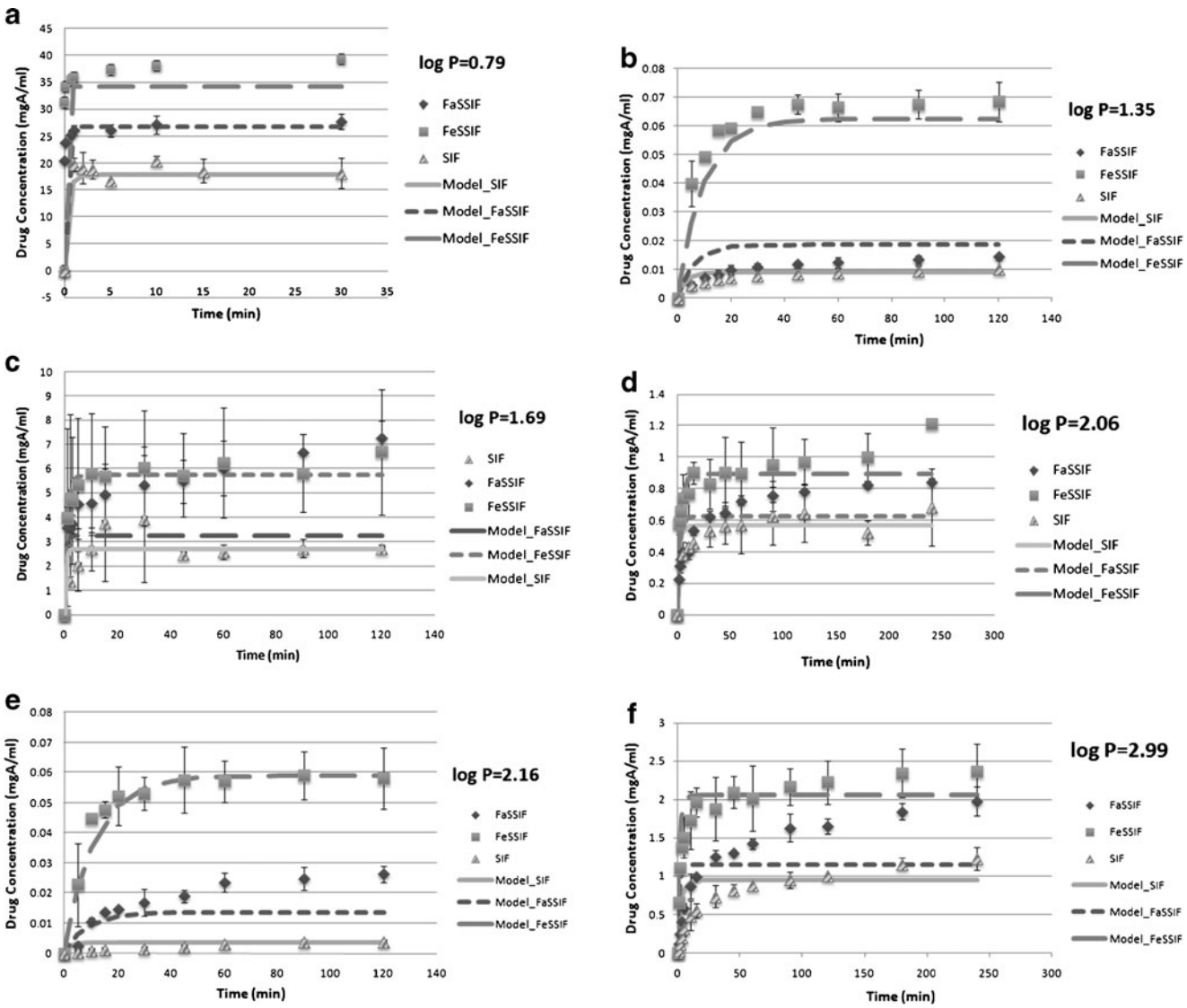

Fig. 4 Comparison of dissolution kinetics of moderate logP compounds, 4-aminobenzoic acid (**a**), dipyridamole (**b**), atropine (**c**), indoprofen (**d**), phenytoin (**e**), 2-naphthol (**f**), haloperidol (**g**), spironolactone (**h**) in SIF, FaSSIF and FeSSIF as well as griseofulvin (**i**) in FaSSIF and FeSSIF with model predictions.

off. This is related to the simple manner in which partition coefficient, K (which ultimately determines the maximum amount of drug that will go into solution), was calculated. The partitioning of drug was assumed to depend on total micelle concentration in solution (Eq. 11), independent of what types of lipids formed the micelles, as different lipid species exist in FaSSIF and FeSSIF at different relative amounts (Table I). Specifically, FaSSIF contains only low concentrations of bile salt and phosphatidylcholine (PC), while FeSSIF contains these components at higher concentrations as well as lipid digestion products (fatty acid and monoglyceride). For some compounds, the simplifying assumption of linear dependence of total drug in solution on total micelle concentration introduced significant error, as was reflected in the lack of a linear fit in Eq. 11 (data not shown), and lack of prediction of the value at which drug concentration leveled off in the dissolution tests. This indicates sensitivity of partitioning to the composition of the micelles in each medium. More specifically, it suggests that some compounds partition favorably into micelles composed of bile salt and PC, while others partition more significantly into mixed micelles also containing fatty acid and monoglyceride (Table III). Thus, more accurate model predictions may result from separate K calculations (and associated measurements) for FaSSIF and FeSSIF. It is also interesting to note that a greater degree of variability is seen in dissolution kinetics in FeSSIF compared to FaSSIF and SIF in some studies (for example, Figs. 2b, 4c–g, and 5a–b).

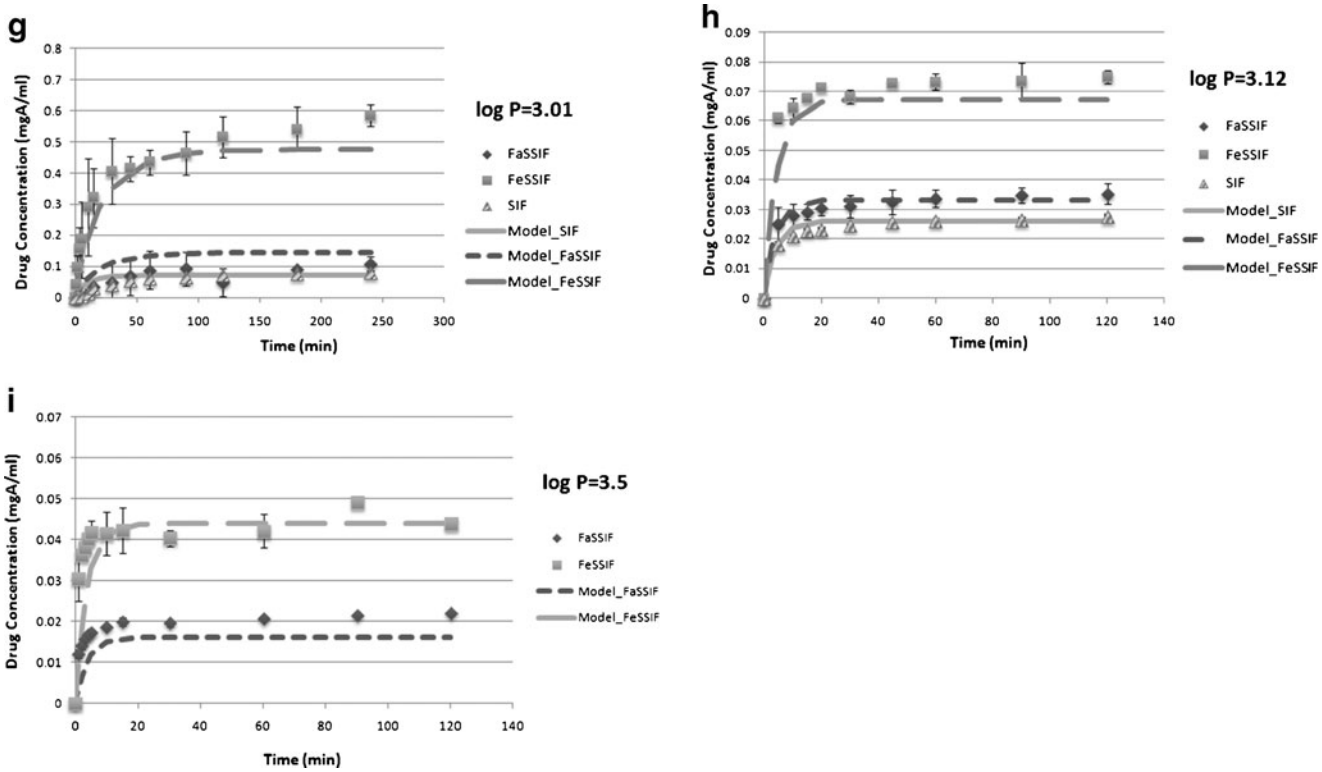

Fig. 4 (continued).

It is possible there is greater sensitivity of dissolution mechanism in micelle-containing media to experimental variability.

Generally good agreement between simulation and experimental results (Figs. 3, 4 and 5) for drug-like compounds with a broad range of properties indicate that food effect on drug dissolution in a simulated intestinal environment can be described by a simple model considering micelle-drug partitioning as a pseudo-equilibrium process and an unstirred boundary layer surrounding dissolving particles across which drugs and micelles diffuse. Most reported studies and development of predictive models of the food effect are based on correlation of compound properties with observed improvement in dissolution kinetics, solubility, fraction absorbed, etc., rather than a mechanistic model (4). It has been noted that a lack of clear correlation between improvement in drug solubility and drug dissolution kinetics in the fed compared to fasted state indicated that a more complex model than the classic Noyes-Whitney drug dissolution expression would be required (22). Drug dissolution in simulated intestinal media has previously been modeled using a Noyes-Whitney type of equation considering only the flux of drug, rather than explicitly considering fluxes of both drug and drug-loaded micelle (8). The improvement in dissolution kinetics in fed-state media was expressed as a change in a fitted kinetic parameter and was interpreted as a reduction in drug diffusivity. It is likely, however, that drug diffusivity when associated with micelles is actually lower than free drug diffusivity given the size of the micelles relative to drug (Eqs. 12 and 13). In general, the classic Noyes-Whitney dissolution expression including a single driving force for dissolving drug dependent upon equilibrium total solubility in the presence of colloids, rather than explicit flux of free and colloid-associated drug, can introduce significant error (13). The advantages of the proposed model include 1) logical mechanistic basis considering improvement in dissolution kinetics due to flux of drug-loaded micelles and 2) requirement to measure only an experimental parameter (partition coefficient) with clear physical meaning in order to make predictions, rather than relying on a fitted parameter.

It should be noted that observing improvement in dissolution kinetics depends on the time scale studied. Compounds for which improvement in dissolution kinetics was observed had relatively slow dissolution rates (comparable to the time scale of the experiments in minutes to hours). For example, when the slow-dissolving phenytoin dissolution test was run (Fig. 4e), the first time point taken at 5 min enabled monitoring of the initial dissolution kinetics. However, for rapidly dissolving 4-aminobenzoic acid, the first time point was 1 min, and no improvement in dissolution kinetics was observed (Fig. 4a). If an earlier time

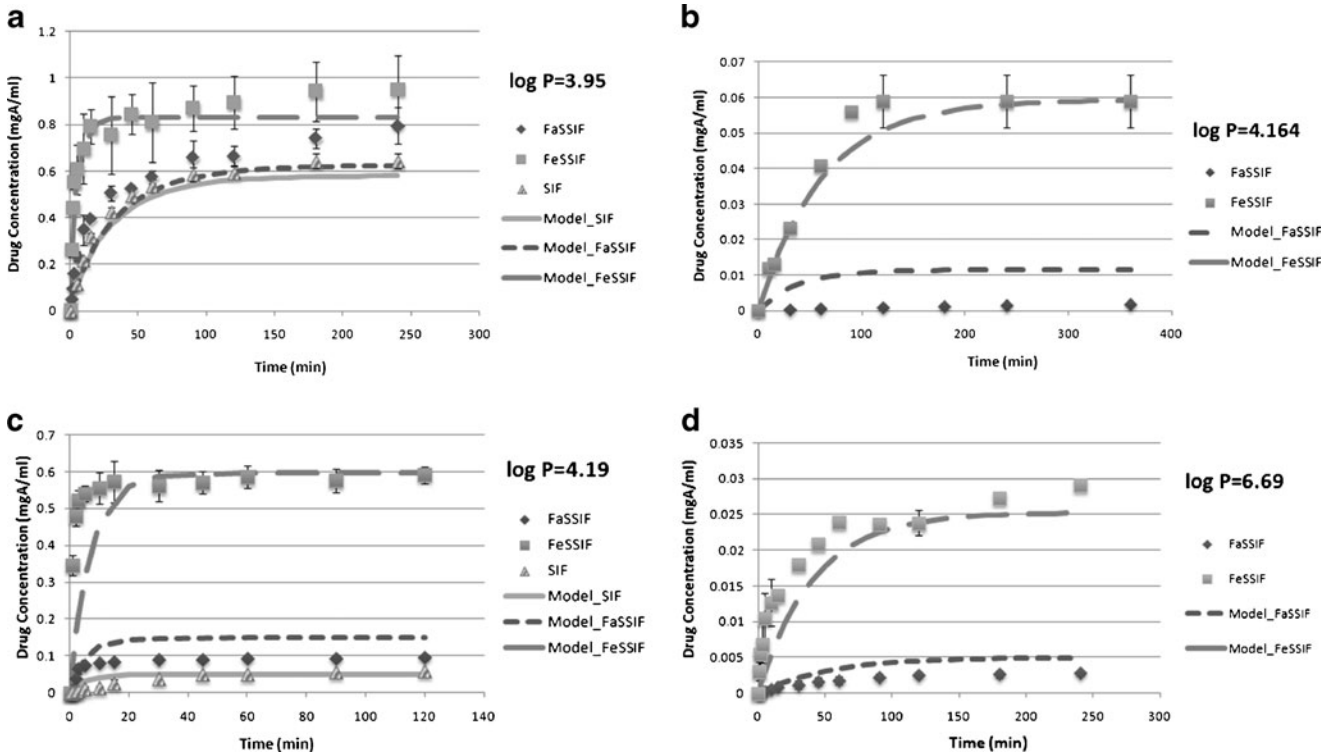

Fig. 5 Comparison of dissolution of phenylbutazone (**a**), fluorene (**b**), iopanoic acid (**c**) and clofazimine (**d**) in SIF, FaSSIF and FeSSIF with model predictions.

point sample had been taken, it might have been possible to observe an increase in dissolution kinetics. The importance of improvement in dissolution kinetics depends on the relative kinetics of dissolution and absorption; if absorption takes place on a time scale similar to or faster than dissolution, the improvement in dissolution kinetics is likely to improve overall absorption and potentially bioavailability. Also, the sink effect produced by more rapid absorption can lead to more rapid dissolution.

After food intake, solubilizing agents such as emulsions, vesicles, micelles, and mixed micelles are formed in the GI tract, all with the potential to affect drug dissolution. A more accurate experimental study and modeling of *in vivo* drug dissolution would consider this complex composition of intestinal fluids and variations with food type. Since biorelevant media are used to mimic the *in vivo* GI tract environment, dissolution kinetics were measured in these media as a starting point for studying and predicting *in vivo* drug dissolution. It is noted that in the biorelevant media employed in this study, particle size measurements indicated that only micelles were formed. In addition, food intake can affect overall drug bioavailability via multiple mechanisms, including increasing drug dissolution kinetics, increasing solubility, altering intestinal transit time, altering intestinal permeability, and enabling lymphatic transport. Thus, the dissolution studies presented here represent a starting point, considering just one of the many factors that should be considered in predicting overall "food effects" on drug bioavailability.

CONCLUSIONS

A model considering the partitioning of drug into micelles as a pseudo-equilibrium process and the flux of both free and partitioned drug in an unstirred film surrounding a dissolving particle surface adequately describes the influence of food-associated micelles on drug dissolution in a simulated intestinal environment. Improvement in drug solubility from fasted to fed state does not substantiate improvement in dissolution kinetics on a time scale relevant to intestinal absorption; both solubility and dissolution kinetics can change oral absorption significantly. Although improvements in accuracy could be achieved by considering particle size distribution and micelle size dependence on drug, the simple developed model appears to be a promising tool in terms of defining *in vivo* dissolution of poorly soluble compounds.

Utilized in a systems-based model of overall drug absorption and pharmacokinetics, this approach may be useful for predicting how the presence of food in the GI tract can affect the bioavailability of drugs.

ACKNOWLEDGEMENTS

The authors would like to thank to Simulations Plus, Inc., Lancaster, CA for financial support and Dr. Robert Campbell from the department of Pharmaceutical Sciences at Northeastern University for particle size measurements.

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